Relating Brain Signal Complexity, Cognitive Performance and APOE Polymorphism – the Case of Young Healthy Adults

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Zusammenfassung

Das menschliche Gehirn ist ein komplexes dynamisches System, dessen Komplexität von großer funktioneller Bedeutung ist und menschliche kognitive Fähigkeiten und deren Störungen charakterisieren könnte. Das APOE ε4 Allel ist ein gut untersuchter genetischer Risiko-Faktor für die Ausbildung der Alzheimer'schen Demenz und für kognitiven Abbau im späteren Leben, Es gibt jedoch noch keine verlässlichen Erkenntnisse zur APOE-Genotyp-Phänotyp-Assoziation bei jungen gesunden Erwachsenen. Das wesentliche Ziel dieser Dissertation ist die Untersuchung der Verbindungen zwischen der Komplexität von Hirn-Signalen, APOE-Genotyp und kognitiver Leistung bei jungen gesunden Erwachsenen unter dem Gesichtspunkt individueller Unterschiede.

Als methodische Vorstudie wurde die Reliabilität der Residue Iteration Decomposition (RIDE) untersucht, eine Methode zur Analyse von Hirnsignalen, die in den Hauptteilen meiner Dissertation eingesetzt wurde. Anhand eines unabhängigen Datensatzes konnte ich zeigen, dass die N400-Komponente (ein Indikator der semantischen Integration während der sozialen Kommunikation) in RIDE-rekonstruierten Ereignis-korrelierten Potentialen (ERP) eine sensitivere Charakterisierung der Autismus-Trait-Ausprägung von Individuen leistet als in konventionell gemittelten ERPs.

In der zweiten Studie wurde untersucht, wie individuelle Unterschiede in APOE Genotypen mit 1) der Komplexität von Hirnsignalen, erfasst durch Multiscale Entropie (MSE), und 2) kognitiven Fähigkeiten in verschiedenen Domänen, insbesondere in der Arbeitsgedächtniskapazität, assoziiert sind. Mit Hilfe von Strukturgleichungsmodellen (SEM) konnten wir zeigen, dass APOE ε4 mit größerer Entropie in Skala 1 bis 4 und geringerer Entropie in Skala 5 und höher assoziiert ist, insbesondere über frontalen Kopfregionen und in Ruhe mit geschlossenen Augen. Zudem konnten wir eine stärkere Abnahme der MSE von der Bedingung mit offenen zu der mit geschlossenen Augen bei ε4-Trägern als bei Nicht-Trägern nachweisen. Die Assoziation von ε4 mit kognitiver Leistung war komplex, aber grundsätzlich scheint ε4 mit geringerer kognitiver Leistung bei Personen mit geringer Schulbildung assoziiert zu sein, während eine vergleichbare Assoziation bei besser Gebildeten nicht nachweisbar war.

Die dritte Studie brachte MSE mit einer anderen Domäne in Verbindung – Gesichter- und Objektkognition. Wir haben dabei gezeigt, dass 1) in allen Skalen erhöhte MSE sowohl mit

besserer kognitiver Leistung hinsichtlich des Diffusionsprozesses bei perzeptuellen Entscheidungen assoziiert ist, als auch mit größerer Genauigkeit. Allerdings waren diese Assoziationen nur für die Bedingung mit geschlossenen Augen konsistent. 2) Erhöhte MSE in den höheren Skalen 7 und 8 war mit einer engeren Koppelung zwischen RIDE-extrahierten Einzel-Trial-Latenzindikatoren der Reiz-Evaluation auf neuronaler Ebene und Reaktionszeiten im Verhalten verbunden.

Zusammenfassend, konnten die Ergebnisse der vorliegenden Dissertation eine Verbindung zwischen der Komplexität von Hirnsignalen, APOE Genotypen und kognitiver Leistung bei jungen gesunden Erwachsenen herstellen. Diese Ergebnisse ermöglichen ein vertieftes Verständnis der Beziehung zwischen Gehirn und Verhalten und stellen eine mögliche Perspektive für die Früherkennung von Demenzen dar, noch bevor ein kognitiver Abbau erkennbar ist.

Schlagwörter: Komplexität von Hirn-Signalen, kognitiver Leistung, APOE, Strukturgleichungsmodellen

Abstract

Human brain is a complex dynamical system, whose complexity could be highly functional and characterize cognitive abilities or mental disorders. The APOE ε4 allele is a well-known genetic risk factor for the development of Alzheimer's Disease and cognitive decline in later human life. However, there are no robust conclusions about the APOE genotype-phenotype associations among young healthy adults. The main goal of this study is to investigate the bridges between brain signal complexity, APOE genotype and cognitive performance among young adults under the framework of individual difference.

Before going deeper to the main topic, the first study assesses the reliability of Residue Iteration decomposition (RIDE), a method for analyzing brain signals that was applied in the main parts of my thesis. Using a dataset independent from the main topic, I demonstrat that as compared with conventional analyzing method, the RIDE-reconstructed event-related-potentials (ERPs), including the N400 component reflecting the evaluation of semantic incongruities during social communication, can more sensitively characterize people across a spectrum of autistic level.

The second study investigates how individual differences in APOE genotypes are associated with 1) brain signal complexity measured with Multiscale Entropy (MSE) and 2) cognitive ability in specific domain, especially, working memory capacity. Using Structural Equation Modelling (SEM) I show that APOE ε4 is associated with higher entropy at scale 1-4 and lower entropy at scale 5 and above, especially at frontal scalp regions and in an eyes open condition; in addition, I show a stronger drop in MSE from closed- to open- eyes condition among ε4 carriers than non-carriers. The ε4 association with cognitive performance is complex, but basically ε4 seems to be associated with worse cognitive performance among lower educated people, whereas no such association appeared among the higher educated.

The third study connects MSE with a different cognitive domain – face and object cognition abilities I show that 1) increased MSE measures at all scales are associated with better cognitive performance from the view of both diffusion process during perceptual decision making and task performance accuracy. However, the associations are only consistent for a closed eyes condition. 2) Increased MSE measures at higher scales (7 or 8) are associated with tighter coupling between RIDE-extracted single trial stimulus evaluation speed at the neural level and reaction time at the behavior level.

To summarize, the results of my doctoral study connect brain signal complexity, APOE genotype and cognitive behavior among young healthy adults, providing a deeper understanding of brain-behavior relationships and - potentially – for early AD diagnosis when cognitive decline is not yet evident.

Keywords: brain signal complexity, cognitive performance, APOE, Structural Equation Model

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Table of Content

List of Abbreviations

AD	Alzheimer's Disease
MSE	Multiscale Entropy
EEG	Electroencephalography
ERP	Event-related potential
SEM	structural equation modelling
ISV	intra-subject variability
RT	reaction time
WMC	working memory capacity
SM	secondary memory
gf	fluid intelligence/reasoning

List of Figures

Figure 2-6. Schematic representation of measurement model for MSE. MSES1-MSES4 are MSE indicators calculated using segments of the whole EEG recording.

Figure 2-7. Reliability of MSE estimated with different data points (data length) for Fz and Pz channel under closed and open eyes resting state condition. (EC – eyes closed condition; EO – eyes open condition).

Figure 3-1. Comparison of conventional ERP amplitude of Cz electrode between congruous and incongruous stimulus under happy and sad condition. (Recalculated from data applied by Lui et al., 2018).

Figure 3-2. Comparison of variance of RT between experimental conditions for each participant. Different rows represent four experimental conditions. Each grid in the figure represents the magnitude of RT variance across trails of each participants.

Figure 3-3. Comparison of conventional ERP and RIDE reconstructed ERP of low AQ participants under happy and sad conditions. ERP wave was calculated as grand ERP by averaging across experimental trails and individuals within each group.

Figure 3-4. Comparison of conventional ERP and RIDE reconstructed ERP of high AQ participants under happy and sad conditions. ERP wave was calculated as grand ERP by averaging across experimental trails within each group.

Figure 3-5. Correlation between ERP difference (properly rescaled by ERP amplitude) and AQ score across participants under time windows: 350 – 600 ms for happy condition and 400 – 650 ms under sad condition. r RIDE: correlation coefficient of RIDE reconstructed ERP difference and AQ score; p RIDE: p-value of RIDE reconstructed ERP difference and AQ

score correlation; r ori: correlation coefficient of original ERP difference and AQ score; p ori: p-value of original ERP difference and AQ score correlation.

Figure 3-6. ERP difference correlation with EQ score across participants under specifically chosen time windows: 350 – 600 ms for happy condition and 400 – 650 ms under sad condition. For abbreviation see Figure 3-5.

Figure 4-1. Schematic representation of higher order latent variable model. Y_1 to Y_9 are observed indicators. η_1 to η_3 are sub-factors which account for common variance among Y_1 to Y_3, Y_4 to Y_6, Y_7 to Y_9. η is the higher order factor which account for common variance among η_1 to η_3.

Figure 4-2. Schematic illustration of latent difference score model representing the difference η_2 subtracting η_1. Double ended arrow represents for the correlation between variables. Regression coefficients on η_2 are fixed to 1.

Figure 4-3. Schematic representation of structural equation model investigating the APOE ε4 association with MSE at each single scale.

Figure 4-4. Topology of APOE ε4 effect size at scale 1-20. Blue color indicated larger MSE value among APOE ε4 carriers, red color indicates smaller MSE value among APOE ε4 carriers.

Figure 4-5. Line plot of grand mean MSE curve with standard error of all participants at F3, F4, FCz and Fz electrodes.

Figure 4-6. Structural equation modelling exploring APOE ε4 association with latent variable MSE AUC score at frontal and parietal ROI. The three indicators Seg1 – Seg 3 AUC scores calculated from MSE curves of each signal segment.

Figure 4-14. Schematic representation of structural equation model (Model 4) exploring the difference between ε4 carriers and non-carriers in the latent factor gf (fluid intelligence).

Figure 4-15. Schematic representation of structural equation model (Model 6) exploring difference between ε4 carriers and non-carriers in the latent factor gf.

Figure 5-1. Schematic representation of the decision process by the diffusion model (Adapted from Ratcliff & Rouder, 1998). 1 represents a quick correct response process with high drift rate and without non-decision time. 2 represents a slow correct response process with non-decision time and low drift rate. 3 represents an incorrect response.

Figure 5-2. Schematic representation of reaction time decomposed by evaluation and response selection and execution.

Figure 5-3. Schematic representation of structural equation model investigating resting state and task state MSE association with diffusion model parameters. FPS – stimulus matching of morphed faces; OPS – stimulus matching of morphed houses; FMS – delayed non-matching to sample with faces; OMS – delayed non-matching to sample with houses; Rest EC 1-4 – resting state eyes closed MSE calculated from EEG session 1-4; Rest EO 1-4 – resting state eyes open MSE calculated from EEG session 1-4; Task Con 1-16 – task MSE calculated from task EEG under condition 1-16.

Figure 5-4. Schematic representation of structural equation model investigating resting state and task state MSE association with face/object task performance accuracy. FMA 1-3: face accuracy task 1-3; OMA 1-3: house accuracy task 1-3; Rest EC 1-4 – resting state eyes closed MSE calculated from EEG session 1-4; Rest EO 1-4 – resting state eyes open MSE calculated from EEG session 1-4; Task Con 1-16 – task MSE calculated from task EEG under condition 1-16.

List of Tables

1. Introduction

The study of human brain is a huge widespread topic which incorporates multiple discipline including neuroscience, psychology, physics, genetics and so on, with the hope to reveal the mysterious brain system and its cognitive foundation. My doctoral study was carried out in such an interdisciplinary research context. By implementing approach under the framework of individual difference, I will investigate the heatedly discussed brain signal complexity, as well as its genetic determinants and cognition ability related consequences.

1.1 Background

In this section, I will review the literature on the mutual association among APOE polymorphism, brain signal complexity and cognitive performance. Moreover, single-trial variability on brain and behavior as well as their relationship will be introduced as property of brain function.

1.1.1 Brain signal complexity

Our brain is the main component of the central nervous system, containing around 100 billions of neurons which are mutually connected in a complex network. All neurons have a resting state activity which can be decreased by net inhibitory input or increased by net excitatory input. Millions of neurons could synchronize and reciprocally act with each other, forming a roaming dynamical system, whose mechanism is crucial in understanding brain function. One important property of the human brain is the fluctuation of brain activity which manifests the complexity of brain signals arising from plentiful neuron coactions. Neuroimaging technologies have visualized the brain signal by varied means, such as Electroencephalography (EEG) which measures the electrical brain activity that could be displayed as voltage fluctuation wave, and functional magnetic resonance imaging (fMRI) which measures the brain activity by the blood flow (blood-oxygen-level-dependent image, BOLD) alteration. The complexity of EEG signal can be characterized by the stochastic oscillations of cross-band-frequency, as well as by the power-law distribution of signal amplitudes. Previous neuroscience studies have provided growing evidence that the complexity of brain signals contains rich information about neural processing (Garret et al., 2013; McDonough et al., 2014; Nakagawa et al., 2013; McIntosh et al., 2013). Thus, there is great significance to study the complexity of brain signals.

Brain signal complexity from viewpoint of dynamical system

The non-linearity of the dynamics exists in both single neuron level and spatiotemporal neural aggregation activities. The neural system resembles physical systems in the way that it can develop multiple activity states at different time points with slight changes of initial input. Noise plays an essential role in the development of the dynamics of such systems. In neural systems, “noise” manifested by the variability or complexity of brain signals originates from various sources such as channel noise, synaptic noise or input noise. Even though not completely understood, in a large number of studies the variability/complexity of brain signals has been demonstrated to be more than simply noise (Garret et al., 2013). Researchers believe that higher variability enhances the robustness of dynamical systems (McKenna et al., 1994), facilitating the adaption of the system to changes of the environment (Basalyga and Salinas, 2006; Faisal et al., 2008). On the other hand, moderate ratio of noise added to a signal would distinguish weak periodic signals from noise and boost the synchronization of neurons (McKenna et al., 1994; Ward et al., 2006).

One theoretical explanation of how brain signal complexity is related to neural processing is that critical states can provide an optimal dynamic range to both weak and strong stimuli and maximize information capacity, namely the number of states that can be accessed by a brain (Shew et al., 2008). Criticality (Bak et al., 1987) of a neural system is a point where neural oscillations are self-organized in biologically realistic networks of excitation and inhibition balance as a response to external input and reflect cost-efficient information processing (Shew et al., 2009, 2011). Therefore, criticality is the optimal state for the brain to process stimulus input and it has been demonstrated that signal variability in the neural system reaches a maximum at this state (Shew and Plenz, 2013; Plenz & Schuster, 2014). According to this theory, the neural system is more flexible to approach multiple states from moment to moment during a critical stage.

Besides rich information contained, variability or complexity of brain signal from thalamus to cortex (Garrett et al., 2018) also reflects functional integration (Tononi et al., 1994; Vakorin et al., 2011; McDonough et al., 2014) of brain. Studies have proposed different predictions about positive (McIntosh et al., 2013) or negative (Ghanbari et al., 2013) relationships between signal complexity and functional connectivity across brain signal frequency bands. But the general believe is that signal complexity positively contributes to functional connectivity. Moreover, recent studies suggested that temporal variability of brain signal is closely coupled

with functional connectivity and decoupled during anesthesia (Huang et al., 2016). Thus, reduction in complexity could be associated with cognitive decline among human beings (Grieder et al., 2018).

Brain signal complexity as foundation of brain function

It is widely accepted among researchers to use brain signal complexity to characterize human brain function, which may not be well captured by mean signals (Garrett et al., 2014). Various studies of brain signal variability have focused on human brain maturation, mental health state and cognitive performance (reviewed by Garrett et al., 2013).

Generally, it is suggested by multiple research works that brain signal variability will increase during human development (e.g. McIntosh et al., 2008; Lippe et al., 2009; Misic et al., 2010) and decrease with aging (Garrett et al., 2010, 2011, Zappasodi et al., 2015), since capability of neural processing could be related to maturation or degradation of neurotransmitters and functional integration (Hasan et al., 2007; Power et al., 2010). Among children it was found that the increase in brain signal variability with age was most pronounced at anterior cortical zones, thus validating the development of functional network during maturation (Miskovic et al., 2016). Garrett et al., (2015) investigated the dopamine versus placebo effect on variability of BOLD signal during cognitive tasks across age groups and showed that the reduction of signal variability during aging may be attributed to dopaminergic change.

Except for age, brain signal variability is also shown to be serve as a biomarker for mental disorder, such as autism, Alzheimer disease (AD), schizophrenia, attention deficit hyperactivity disorder (ADHD) and so on (Takahashi et al., 2012; 2016; Nomi et al., 2018). There is long history of studies on the association between signal complexity and AD. In an earlier EEG study, Woyshville and Calabrese (1994) found that AD is related to complexity of cortical dynamics underlying EEG, because decreased correlation dimensionality was found within the occipital area.

In some of the studies, neural recordings were carried out on participants while they were performing specified cognitive tasks and the complexity of their recorded brain signals was analyzed and thus linked to their cognitive performance. McIntosh et al. (2008), showed that a measure of signal variability in EEG during face memory tasks was higher in young adulthood than in teenagers. In other words, signal variability increased with brain maturation.

It was concluded that brain signal variability may increase during human maturation from infanthood to early childhood (De Wel et al., 2017; Lippé et al., 2009). Moreover, McIntosh et al. (2008) suggested a positive correlation between brain signal variability and behavioral stability as indicated by smaller trial-to-trial behavioral variability; this association was confirmed by Raja Beharelle et al. (2012).

Multiscale entropy is widely used to indicate signal complexity

In the measurement of brain signal complexity, entropy is a widely used concept (e.g., Pincus & Goldberger, 1994; Kaplan et al., 1991). It quantifies the complexity of signals as irregularity and number of patterns detected in the signal (Pincus & Goldberger, 1994). In psychophysiological studies, different types of entropy measurements have been applied in various neuro-imaging signals such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) (e.g., Gómez C et al., 2013; Mizuno et al., 2010; Sokunbi et al., 2013). Traditional measurements include approximate entropy (Pincus, 1991) and sample entropy (Richman & Moorman, 2000). Figure 1-1 gives example of EEG recordings of two people with low and high entropy.

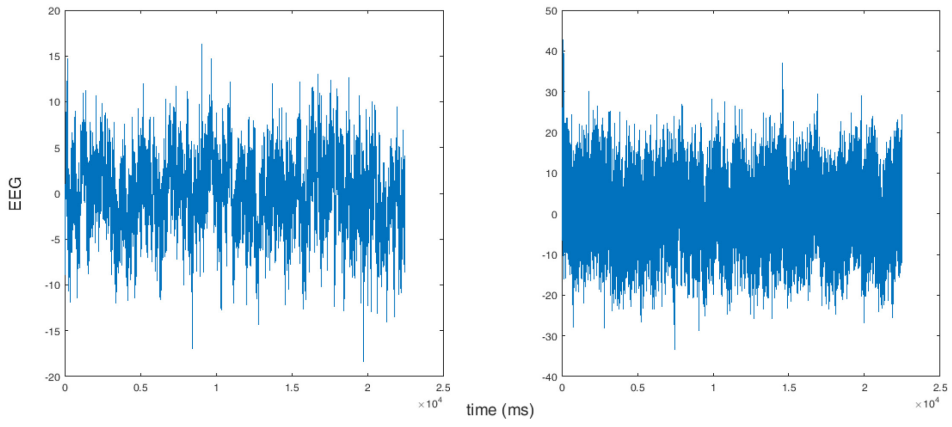

Figure 1-1. Two examples for EEG recording of participants with low (left) and high (right) Sample Entropy.

A recently developed measure, Multiscale Entropy (MSE, Costa et al., 2002a; Costa et al., 2005), is now one of the most popular approaches in studies on brain signal complexity. The advancement of MSE measurement as compared with traditionally used entropy parameters is that it allows investigating entropy of temporal EEG signals from original high-frequency series to coarse-grained low frequency series, thus while repeated patterns at different

temporal scales could be detected (Costa et al., 2005). Thus, it provides a measurement of "real complexity" in datasets deviating from linearity, periodicity, as well as simple randomness in multiple time scales. In the past decade, MSE has been regarded as a more reliable description of complexity of the stochastic EEG signals.

While MSE has been successfully applied in studies of brain signal complexity (e.g., Li et al., 2018; Takahashi, 2016, McIntosh et al., 2014) during the past years, the methodology is not flawless. Since MSE measures the entropy of data series basing on multiple temporal scales, the coarse graining process of the time series data would require the original data series to be long enough, otherwise unreliable or even undefined entropy measurement would ensue (Humeau-Heurtier et al., 2015; Wu et al., 2013). Therefore, methodology improvements based on MSE were also proposed. Representative measurements which had been applied on experimental data include Refined Multiscale Entropy (Valencia et al., 2009); Composite Multiscale Entropy (Wu et al., 2013); Modified Multiscale Entropy (Wu et al., 2013), and so on. These improvements were superior in considering the reliability issue. In my thesis project, the original MSE will be a major measurement to be applied. The detailed algorithm will be introduced in the methodology section. In order to account for the reliability issue of MSE estimation, different data length with their corresponding estimation reliabilities were also compared.

Since MSE is a measurement superior in assessing sample entropy at multiple time scales, the biological meaning of low (fine) and high (coarse) scales might be different, indicating different neural processing levels (McDonough and Nashiro, 2014). By applying the entropy measurement on multiple time scale, the predictability (regularity) of the time series could be altered across scales. The MSE vs time scales curve calculated from EEG signal usually yields a peak where the sample entropy is maximized, indicating that the predictability of time series could first increase then decrease with change of scale factor. For example, elder people with declined cognition performance as compared with younger may be characterized by smaller MSE at higher scales and larger MSE at lower scales (McIntosh et al., 2014; Sleimen-Malkoun et al., 2015). The inversed correlation from low to high scale might be related with different frequency bands. Increased lower scale MSE representing high frequency wave complexity suggests enhanced local-level neural processing, while higher scales are more related to global-level processing (Vakorin et al., 2011; McIntosh et al., 2014; Grundy et al., 2017). Even though there is not yet a clear definition of the term "complexity",

it is suggested that the evaluation of complexity should be based on correlation across multiple scales (Costa et al., 2002b; 2003a, 2003b) so as to address the "meaningful structural richness" (Grassberger, 1991). Therefore, when investigating MSE of brain signals, it is crucial to interpret the results depending on temporal scales.

1.1.2 Resting state brain signal complexity and individual difference in cognitive ability

Brain signal time series can be measured both during resting states and task processing. Even though during resting state when no task is being processed by the neural system, the spontaneous brain activity still displays nontrivial patterns. In contrast to task-related brain activity, the brain activity during resting state could be wondering in the state space which could correspond to ongoing cognitive process (Barttfeld et al., 2015). Thus, resting state brain activity could represent background brain state, and the complexity of resting state brain signals may result from stochastic neural processing, as well as the interaction among neurons in the complex brain network (Faisal, Selen, & Wolpert, 2009) at default state. Therefore, resting state brain signal complexity could be viewed as a personal trait, thus providing a relevant measurement for individual difference in cognitive ability (Mohr & Nagel, 2008).

Available studies on the relationship between resting state brain signal variability and cognitive ability were carried out across age, since aging usually results in cognitive decline. In a study by Sleimen-Malkoun et al. (2015), a range of variabiltiy measurements including MSE were applied on resting state EEG of both elder and younger groups. Results implied that elder people have larger complexity at low time scales and lower complexity at high time scales.

Most of the existing studies on resting state brain signal complexity are focused on its direct link with aging or mental disorder, which may result in diminished cognitive ability. The assocation between resting state brain signal complexity and cognitive ability is therefore not straightforward, but commonly mediated by age or disorder. So far, few studies have focused on the resting state brain signal complexity and its association with psychometric cognitive measurements among young healthy people, so as to directly build connection between these two personal traits across normal individuals. The investigation of this connection, however, could be crucial for providing support for early diagnosis in mental disorder when the cognitive decline is not yet clearly detectable.

1.1.3 Intra-subject variability in ERP and behavior

When carrying out multiple-trial psychophysiological experiments, there are no two trials with exactly identical recordings. The variability in neural and behavioral recording across trials, referred to as intra-subject variability (ISV) may reflect the stability of cognitive sub-processes, rather than simply measurement error. Therefore, in addition to average performance, the study of ISV has received increasing interest during recent years. In psychological and neuroscience studies, ISV has been studied mainly in two aspects: the event-related potential (ERP) and the reaction time (RT). ERP is EEG-recorded electrical brain response that results from particular stimulus. It is a valid measurement when studying brain function. RT refers to the time when behavior response take place after stimulus. Figure 2 gives a representation of stereotype of ERP and reaction time. The dominant wave is called ERP component, it is related with the central processing of particular stimulus. For example, a negative wave component that occurs at around 150-200 ms is called N170 component, which reflect the brain response to a face stimulus (Bötzel et al., 1995).

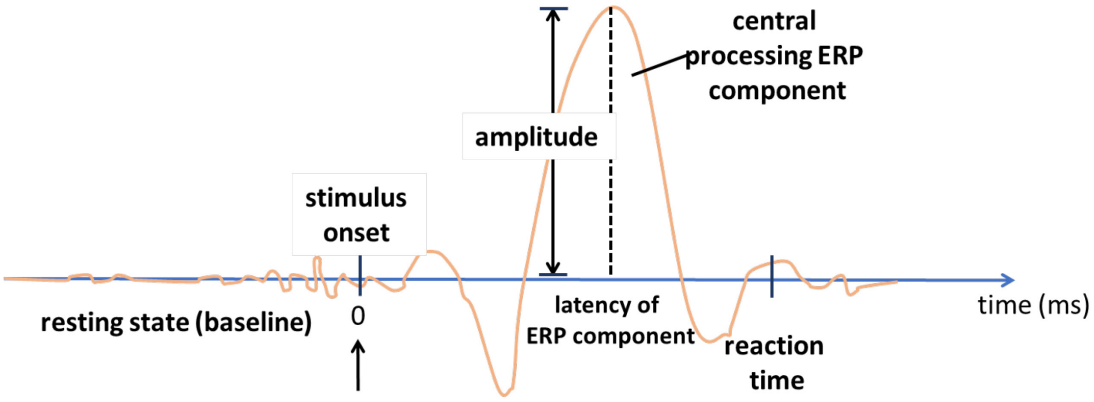

Figure 1-2. Schematic illustration of ERP and reaction time in EEG recording.

ISV in ERP

In some recent work, ISV in ERPs was shown to be related with ISV in behavior. The observed ISV variability in ERP might result from the stochastic biological and information processing mechanisms of neurons, and their interactions in complex brain networks (Faisal et al., 2009). However, traditional ERP studies have mainly focused on averaged ERPs across many trials. Such averaging ignores single-trial information, but ERP measurement on a trial-by-trial basis is a difficult endeavor.

Ribeiro, Paiva, & Castelo-Branco (2016) studied the ISV of sensory processing-related ERPs and described its contribution to reaction time (RT) variability. Yet, there is not sufficient evidence on the relationship of ISV of ERPs and ISV in cognitive performance. Bender et al. (2015) calculated both, inter-trial and spatial (topographic) variability of specific ERP components, while only spatial variability was shown to predict reaction time fluctuations. Saville et al. (2015) examined ISV in the latency of the P3b component of the ERP in healthy persons with ZNF804A gene polymorphism and compared it with behavioral ISV, finding that even though the ISV of P3b latency was different between two genotypes, the ISV of behavior was not significantly different. This finding indicated that ISV of ERP is more sensitive to reveal genetic influence on cognitive processes. In another study Saville et al. (2012) related the standard deviation (SD) of RT with ISV of the P3b component and reported a sizeable positive correlation.

ISV in behavior

Similar to brain studies outlined above, also purely behavioral studies focused mainly or solely on the average performance speed and accuracy by computing the mean RT or frequency of correct responses across multiple trials. However, in terms of characterizing performance optimization, cognitive behavior should not be only evaluated by mean speed and accuracy, but also by trial-by-trial variability, with lower variability indicating more stable performance (McIntosh et al., 2008). For example, the ISV of RT measured in subjects suffering from brain injury (Stuss, et al., 2003) or attention deficit disorders (Klein et al., 2006) is larger than variability in healthy controls. Further, an increase in ISV of RT with aging (Schmiedek et al., 2009) goes along with the well-documented cognitive decline with aging. Using a linear mixed effect model, Schmiedek and colleagues (2009) showed that ISV in RT may indicate substantial information related to cognitive ability beyond the mean RT. In a study by Saville et al. (2011), ISV of RT was further established as a stable trait. In more recent studies, the commonality in this trait between individuals with, for instance, autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) was applied as a biomarker for investigation of the similarity in underlying mechanism of these mental disorders (Adamo et al., 2014).

Even though there is vast evidence indicating that the average individual performance is significantly affected by brain signal activity, the variability of behavior across trials was usually ignored, and hitherto only first attempts of inclusion of ISV exist. In my study, the

ISV of behavior, rather than the average performance, will be prominent indicators of the individuals' cognitive abilities.

1.1.4 APOE gene polymorphism

The APOE gene lies on the 19th chromosome and is known to instruct the formation of Apolipoprotein E, a cluster of apolipoprotein that combines fat and fosters the process of keeping cholesterol in the human body at a normal level. There are three versions (alleles) of the APOE gene: e2, e3 and ε4. These alleles can combine to three homozygotic (e2/e2, e3/e3 and ε4/ε4) and three heterozygotic (e2/e3, e2/ε4 and e3/ε4) genotypes. It is well known that APOE ε4 allele is the strongest genetic risk factor for developing Alzheimer Disease (AD) in later life (Farrer et al., 1997). In recent years, neuroimaging techniques (e.g., EEG, fMRI) have provided evidence that APOE ε4 allele could induce decreased brain activity and cognitive decline. This evidence stems mainly from studies focusing on elder people. Among young healthy people, contradictory findings regarding APOE associations with brain activity or cognitive performance exist, which lead to heated discussion on whether APOE genotype-phenotype association could have already been notable when AD trait in behavior is not visible yet.

APOE genotype effect on cognition performance

It is well studied that APOE ε4 allele exerts detrimental effect on general cognitive performance on non-demented elder people, so that they would perform inferior in cognition behavior such as episodic memory and executive functions (Small et al., 2004; Wisdom et al., 2011). However, among young healthy APOE ε4 carriers, better cognitive performance was reported for episodic memory (Mondadori et al., 2007), processing speed (Marchant et al., 2010), decision making (Marchant et al., 2010), prospective memory (Evans et al., 2013), verbal fluency (Marchant et al., 2010; Alexander et al., 2007; Marioni et al., 2016), intelligence (Yu et al., 2000) and so on. Oriá et al. (2005) also found better verbal fluency among children who were APOE ε4 carriers as compared with non-carriers. It has been suggested that the better performance of young ε4 carriers may represent a case of antagonistic pleiotropy (e.g., Han & Bondi, 2008), which means that an allele could control separately for positive and negative trait for the fitness of human beings (William, 1957) during their early and later life.

Nevertheless, the antagonistic pleiotropy hypothesis of APOE ε4 allele has been challenged by many studies, such that no better (Matura et al.,2014; Dowell et al., 2013; Dennis et al., 2010), or even worse cognitive performance (Eramudugolla et al., 2014; Bloss et al., 2008) was detected among young APOE ε4 carriers. As summarized by a meta-analysis (Ihle et al., 2012), inconsistent results from literature could be attributed to the fact that the specific cognitive facets varied across studies. According to another recent meta-analysis (Weissberger et al., 2018), only executive functions out of several different cognitive domains were found to be better among ε4 carriers than non-carriers. Moreover, Rusted & Carare (2015) proposed that the inconsistency could also arise from interaction effect between APOE genotype and cholesterol transport, neuronal repair or brain structure impairments (Kunz et al., 2015).

Besides these physiological factors, environmental factor, such as education level plays important role in modulating cognition (Arenaza-Urquijo et al.,2013) and also preventing people from developing AD in later life (Valenzuela & Sachdev, 2005). For example, in the study by Arenaza-Urquijo et al. (2013) with wide age range, higher educated ε4 carriers may have delayed cognitive decline. Therefore, when investigating relationship between gene and cognitive behavior, interactive effects of education level should be taken into consideration.

Working memory is a very important facet of cognitive function. It assesses the capability of the neurocognitive system to temporally store information for later processing (Miyake et al., 1999). A wide collection of cognitive tasks has been proved to capture this cognitive capacity. In previous studies, n-back task was one of the most widely used measurements of working memory (e.g., Sinclair et al., 2015). Other task measurements include complex span (Estévez-González et al., 2004), updating task (e.g., Velichkovsky et al., 2015; Reinvang et al., 2010) and so on. As suggested by theoretical behavioral studies, secondary memory (SM), or long-term memory should be considered as a component of working memory system (Unsworth et al., 2014; Shipstead et al., 2014). According to a study by Wolk et al. (2010) on APOE association with long-term memory, declined memory retention was detected among elder ε4 carriers. Similar result was suggested by a recent study (Zokaei et al., 2019) on elder participants. Additionally, literature further suggested the isomorphism between WMC and fluid intelligence (Kyllonen and Christal, 1990; Süß et al., 2002), which is a concept referring to logical thinking and problem-solving ability without contribution from acquired knowledge. In contrast to result about secondary memory, Woo et al. (2017) found no difference in fluid intelligence between APOE ε4 carriers and non-carriers.

To summarize, WMC is an essential cognitive domain, which should be studied along with secondary memory and fluid intelligence. Contradictory evidence exists on whether young APOE ε4 carriers perform better or worse in these capacities. This motivates studies with latent variables to generalize the common variance among these cognitive facets.

APOE genotype effect on brain activity

Regarding to brain activity of young healthy adults, the role played by APOE ε4 is also not definite yet, even though studies on elder non-demented people suggested altered brain activity, such as reduced glucose metabolism (Reiman et al., 1996; Small et al., 1995) and resting state functional connectivity (Sheline et al., 2011) among ε4 carriers. This evidence may explain the robust findings of inferior cognitive performance among elder ε4 carriers. Comparatively, studies on young healthy adults proposed that there might be compensatory mechanism of APOE ε4 on brain structure, thus resulting in similar or even better cognitive performance (Kunz et al., 2015; Bookheimer et al., 2000; Filippini et al., 2009). According to these findings, young APOE ε4 carriers have increased hippocampal activity (Kunz et al., 2015; Bookheimer et al., 2000); greater blood oxygen level dependent (BOLD) responses at bilateral medial frontal and parietal cortex (Bondi et al., 2005; Wishart et al., 2006).

APOE genotype effect on brain signal complexity

Besides existing studies investigating the relationship between APOE ε4 on brain activity, previous studies were also interested in whether brain signal variability/complexity could differ between ε4 carriers and non-carriers. As a widely-used measurement for brain signal complexity, Multiscale Entropy (MSE) has been applied to distinguish APOE gene related neurodegenerative diseases, say, Alzheimer Disease (AD) (Abásolo D et al. 2006; Dauwels et al., 2011).

As mentioned above, even though not very well understood yet, the physiological meaning of lower and higher temporal scale MSE of brain signal might be different. Mizuno et al. (2010) used MSE to characterize EEG complexity of AD patients and healthy controls. According to his study, AD patients have smaller MSE at lower scales and larger MSE at higher scales as compared with healthy controls. Similar results were found by Escudero et al. (2015) by applying “refined composite MSE”, which is a developed MSE measurement, on MEG signal. As indicated by more recent fMRI studies, decreased brain signal complexity was detected

among AD patients (Grieder et al., 2018; Li et al., 2018). Unfortunately, there is lack of evidence supporting relationship between APOE ε4 and MSE among young healthy people, especially MSE calculated for EEG signal. An fMRI study by Yang et al., (2014) failed to detect APOE ε4 association with BOLD signal complexity among young adults, even though reduced complexities were found among elder ε4 carriers. However, study on such association may provide knowledge for early detection of AD disease. Similar to cognitive performance, MSE could also provide reference for phenotype difference at young adulthood, even act as a biomarker for AD risk when behavioral performance is not yet detectable.

1.1.5 Structural Equation Modelling in individual difference study

In multiple fields of psychological study, Structural Equation Modelling (SEM) is a widely applied method to analyze the relationship among underlying constructions that are not directly measurable, but possible to be measured indirectly by related observed variables. It is a method combining Factor Analysis and Regression, enabling more flexibility to the analysis of data than either of these two techniques alone. Early at the beginning of 20th century, factor analysis was introduced by Spearman (1904), who proposed a latent "general intelligence" construct indicated by broad specific mental task abilities. During the last century, the methodology has been developed into a family of related methods, rather than a single technique.

Besides traditional psychometric and personality studies, SEM has been increasingly applied to neuroimaging data to address the topic of individual differences. In current neuroscience studies, simple correlation measures (Pearson or Spearman) were more widely applied especially in fMRI study of brain-behavior relationship (e.g., Lebreton and Palminteri, 2016). Comparing to simple correlational analysis, SEM is superior in not requiring the random measurement error assumption and because itprovides path to addressing source of systematic error (Cooper et al., 2019). There are already some emerging studies using SEM to explore individual differences in brain-behavior relationships, yet there are some concerns on the inappropriate usage of this scheme as summarized by Cooper et al. (2019). For example, some of the studies were more focused on the context of dependency between connectivity and cognitive function but failed to address the question of individual difference (McIntosh et al., 1996).

In individual difference study, the application of SEM can be roughly divided into two groups. One of them is the validity study based on measurement models. Using Confirmatory Factor Analysis (CFA) which is one modelling approach in the SEM family, one can decide whether the common property (between-subject variance) of a cluster of physiological or psychometrical measurements could be captured by an underlying latent construct. For example, some previous works have successfully suggested that the frontoparietal network have sub-region controlling different processing roles rather than being a united network (Gratton et al., 2016). Another group is the correlation study, which investigates the relationship among latent constructs. For example, one recent study by Bolt et al. (2018) implemented SEM method to investigate the dependency of individual difference in brain-behavior relationship on local or global brain network. The detailed implementation of SEM will be introduced in the method description session.

1.2 Open questions and research objectives

So far, the literature gap exists at several aspects: Firstly, even though large number of studies were interested in the cognitive determinant of APOE genotype, there was controversial conclusion towards the brain signal complexity and cognitive performance of young healthy APOE ε4 carriers. Secondly, as a widely applied measurement of brain signal complexity, MSE estimation for characterizing cognitive performance was largely based on brain signal measured during task, rather than resting state. Thirdly, we hypothesize that resting state MSE could be viewed as a personal trait that modulates cognitive ability, yet its association with brain-behavior relationship during cognition tasks has not been investigated.

Therefore, my study aims to investigate the following questions:

1) How does APOE ε4 allele account for the cognitive performance of young healthy adults?
2) How does APOE ε4 allele account for the MSE-measured brain signal complexity among young healthy adults?
3) How does MSE characterize the cognitive performance and the brain-behavior relationship during cognitive task?

The significance of studying questions 1) and 2) is that it may provide evidence whether the carriers of AD risk factor (APOE ε4) already shows altered phenotype at neural (brain signal

complexity) and behavior (cognitive task performance) level when the AD related neurodegeneration was not visible yet. To incorporate question 3) with 1) and 2) in an integrated picture, a two-level modeling and analysis framework could be constructed. Level one is the within-subject level, which includes measurements of multiple signal trails of ERP and reaction times within each subject. Level two is the between-subject level, each subject has one unique measurement at this level, such as APOE genotype and MSE measurement. Figure 1-3 gives an illustration of my research questions.

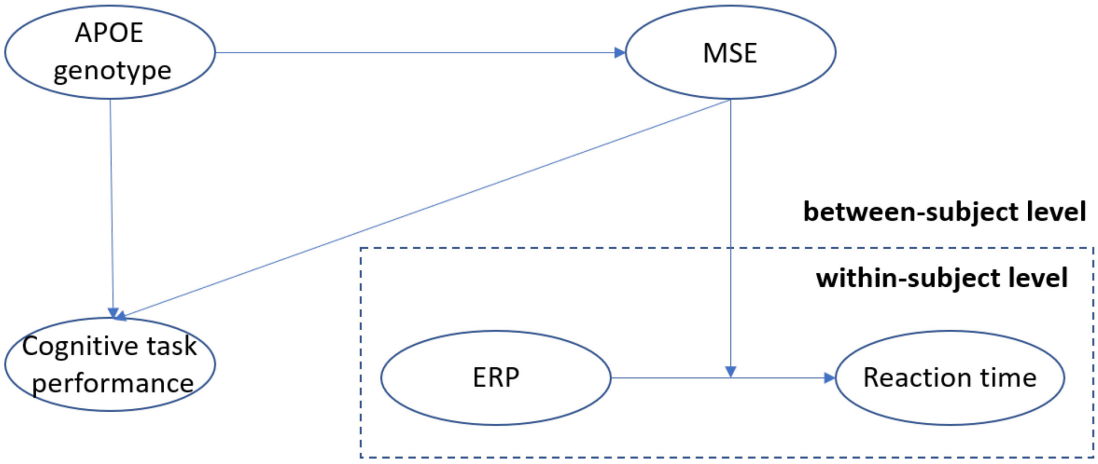

Figure 1-3. Schematic illustration of research questions. At within-person level in the dashed box, ERP measured on each signal trial is supposed to mediate the single trail reaction time. At between-person level, individual difference in APOE genotype may be associated with both cognitive ability and MSE. MSE may be further associated with cognitive ability.

2. Datasets and Methodology

In this chapter, the main data collection procedure, the datasets and data analysis methods I used in my doctoral study will be briefly introduced. Since my work is basically focused on data analysis and modelling, I will introduce Multiscale Entropy (MSE) and Residue Iteration Decomposition (RIDE) methods for EEG data analysis, as well as Structural Equation Modelling (SEM) for statistical modelling.

2.1 Datasets

All the studies in my doctoral thesis were based on datasets collected by my colleagues from Germany with their permissions. Since my study was focused on gene, brain and behavior relationship among healthy young adults, these datasets were separately collected but largely overlapping in certain measures such as APOE genotyping, EEG recording and cognitive tasks. The age of the samples all ranged between 18-40 and all participants were native German speakers and had no cognitive disorders. Statistics of education and genotype is described in Figure 1 and Figure 2. Here I will introduce the available measurements of these datasets relevant to my study and describe how these datasets were used separately or in combination in my study.

Sample 1: Ulm data 1. This sample included 255 young adults, who accomplished a series of working memory, secondary memory and reasoning tasks without EEG recordings. Details of these tasks will be described in Chapter 6.2. Among them 245 participants also had APOE genotype recordings and were used for analysis in my study. 56% of the participants in the sample were female.

Sample 2: Ulm data 2. This sample included 324 participants who completed the same working memory task as one of the working memory tasks completed by sample 1. Among the 324 participants only 225 (78% female) had APOE genotype recordings. The working memory tasks completed by this sample was the same as part of the working memory tasks in sample 1 (as displayed in Table 1), but each task was divided into three sessions with different difficulty loadings.

Sample 3: Greifswald data. This sample included 99 participants with both working memory tasks and resting state EEG recordings. The working memory tasks were identical to that in

sample 2. The EEG recording included 90 s of open eyes resting state, while participants were instructed to do noting with their eyes open, as well as 90 s of closed eyes resting state. Among the 99 participants 70 (56% female) had APOE genotype recordings, and these 70 participants were included in the dataset to be analyzed.

Sample 4: Berlin data 1. This sample included 244 young participants (50.8% female) with APOE genotype recordings, who also completed a series of emotional perception, face cognition and fluid cognitive abilities. The fluid cognitive ability (reasoning ability) measurements were used in my study.

Sample 5: Berlin data 2. This sample included 206 participants with their APOE genotype available. Both EEG and psychometric recordings were available to be applied in my study. The EEG session included 1) resting state closed and open eyes EEG recording, 90 s each as sample 3. 2) EEG and reaction time recorded during face cognition task under 16 different conditions (detail of different task conditions will be described in Chapter 5). 72 experimental trials were carried out under each condition, giving 72*16 experimental trials in total for each participant. 3) psychometric measurements on face/house cognition as well as fluid intelligence (reasoning) measurements. Details of these psychometric tasks will be described in Chapter 5.

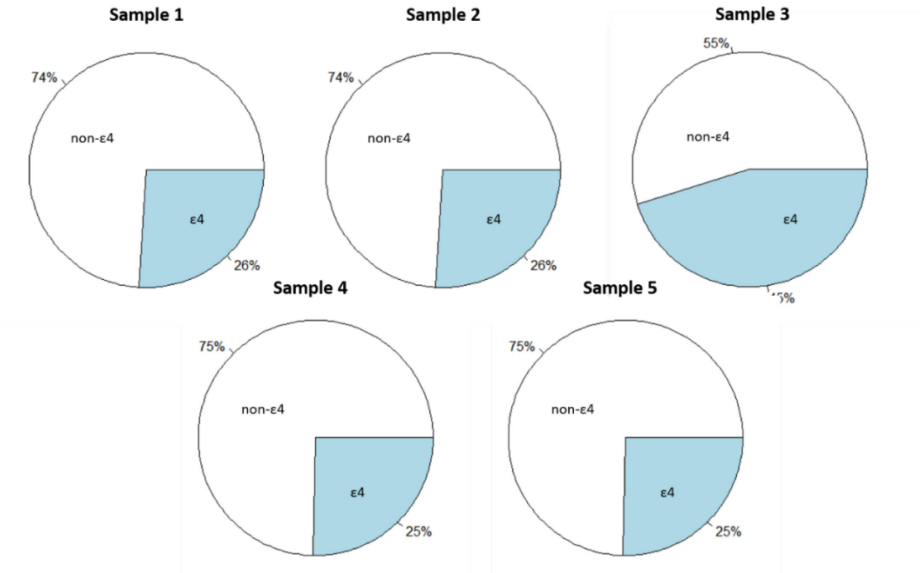

Figure 2-1. Frequency distribution of APOE genotype of samples 1-5

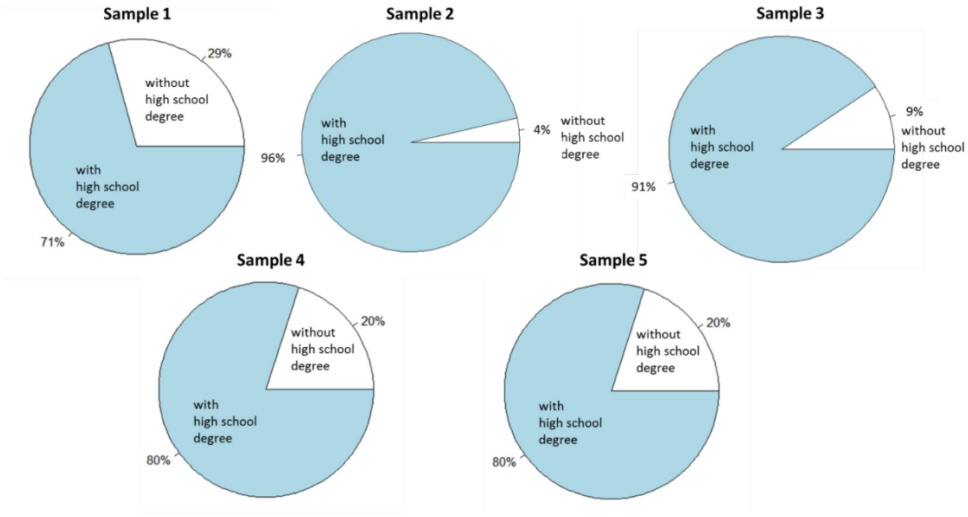

Figure 2-2. Frequency distribution of education level of samples 1-5.

Table 2-1 Measurements of all samples applied in my doctoral study

Measurements		Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
EEG recordings						
Under open eyes resting state				✓		✓
Under closed eyes resting state				✓		✓
During task						✓
Psychometric measurements						
Working memory tasks	Letter-color binding (Bind_lc)	✓				
	Word-numbering binding (Bind_wn)	✓				
	Locating-letter binding (Bind_ll)	✓				
	Verbal updating (Upd_v)	✓				
	Numerical updating	✓				

	(Upd_n)					
	Spatial-figural updating (Upd_f)	✓				
	Verbal recall 1-back (RNb_v)	✓	✓	✓		
	Numerical recall 1-back (RNb_n)	✓				
	Spatial-figural recall 1-back (RNb_f)	✓	✓	✓		
	Reading span (CSpan_v)	✓				
	Operation span (CSpan_n)	✓				
	Rotation span (CSpan_f)	✓			✓	
	Memory updating (MU)				✓	
Secondary memory tasks	Word-word secondary memory (SM_v)	✓				
	Word-number secondary memory (SM_n)	✓				
	Letter-position secondary memory (SM_f)	✓				
Fluid intelligence (reasoning tasks)	Verbal fluid intelligence (gf_v)	✓				
	Numerical fluid intelligence (gf_n)	✓				
	Figural fluid intelligence (gf_f)	✓				
	Raven's progressive matrices (Rav)				✓	✓

Face/house cognition tasks	Morphed face/house (FPS/OPS)		✓
	Delayed matching face/house (FMS/OMS)		✓
	Learning/recognition of face/house (FMA1/OMA1)		✓
	Decay rate face/house (FMA2/OMA2)		✓
	Eyewitness testimony of face/house (FMA3/OMA3)		✓

As summarized in Table 1, sample 3 and sample 5 had EEG recordings. The procedures of resting state closed and open eyes EEG recordings of the two samples were the same and therefore could be analyzed as a combined sample. Sample 1 had multiple working memory, secondary memory and fluid intelligence task recordings. Sample 2 and 3 had identical working memory recordings. Sample 4 had two working memory measurements that overlap with sample 1 and one reasoning measurement. Sample 5 had one reasoning measurement identical to sample 4, but separate into three sessions.

The above samples were used in my doctoral study described in Chapter 6 and 7. In Chapter 6 which included two studies 6.1 and 6.2 that were related to each other, resting state EEG recordings of sample 3 and 5 were analyzed as a combined sample in 6.1; in study 6.2, working memory, secondary memory and reasoning measurements in sample 1-5 were analyzed as 4 independent samples with sample 2 and 3 combined into one integrate sample. In Chapter 7, both EEG and face/house cognition task recordings of sample 5 was used for analysis.

2.2 Methodology

In this section, I will briefly introduce the major novel methodologies for data processing and analysis in my studies: Residual Iteration Decomposition (RIDE), which is developed by the group of my supervisors for ERP analysis; Structural Equation modelling (SEM), which is complex statistical modelling widely applied in psychological research; and Multiscale Entropy (MSE), which is an indexation of brain signal complexity.

2.2.1 Residue Iteration Decomposition – methodological advances in ERP analysis

As argued in the introduction (Chapter 1), in cognitive experiments, there is considerable variability in reaction time across trials, and it is conceivable that brain response in cognitive sub-processes may also have different extents of trial-by-trial latency variability. Event related potential (ERP) analysis is a useful tool to study the neural process after stimulus. One limitation is the noise across multiple experimental trials. Conventional ERP analysis scheme is to average out the noise and only leaving the average ERP components for analysis. However, this averaging scheme is stimulus- or response-locked, therefore smearing the peak amplitudes of ERP components with latency jitter (see illustration in Fig. 2-3). Moreover, the conventional averaging scheme omitted the variability in single trial ERP amplitudes and latencies, which could contain substantial information related to performance variability.

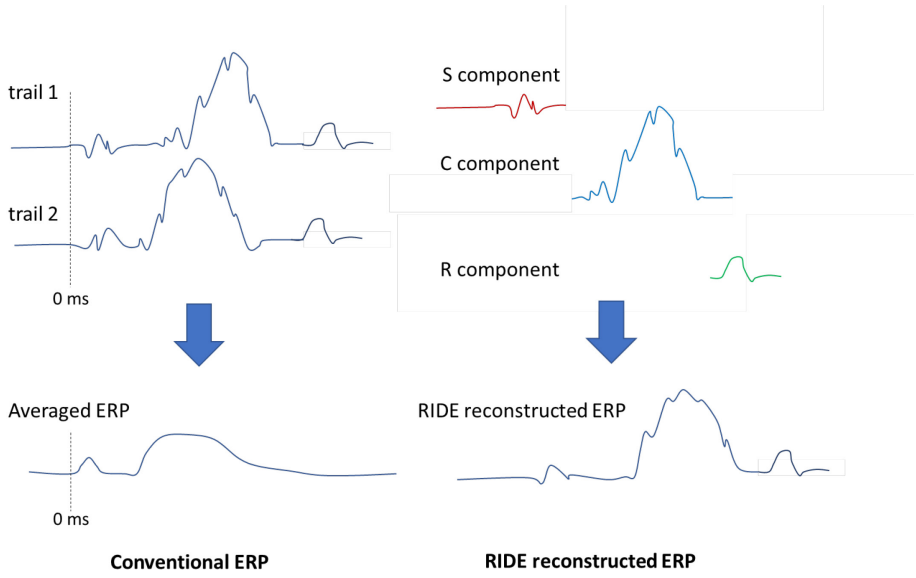

Figure 2-3. Schematic representation of conventional ERP averaging scheme (left panel) and RIDE (right panel). Conventional ERP averaged locking to stimulus had blurred central processing component due to variability in trail to trail latency. RIDE reconstructed ERP overcomes this problem after decomposing the ERP into S, C and R component clusters and correcting for latency jitter by realigning the components.

In my doctoral study, the above limitation could be overcome by the application of Residue Iteration Decomposition (RIDE; Ouyang et al., 2011). Unlike the conventional averaging scheme where trials were simply aligned by stimulus time (Figure 2-3 left panel), the basic idea of RIDE is to separate ERPs into a stimulus-locked (S) component cluster whose latency is set to stimulus onset time, a response-locked (R) component cluster whose latency is locked

to reaction time and a central (C) component cluster including the rest of components lacking explicit latency information (Figure 2-3 right panel). C typically captures the decision-making sub-process between signal perception (S) and response execution (R), and has been found to closely relate to the P3b component of the ERP (Ouyang et al., 2011, 2013). The principle of the method is to iteratively estimate the latency of the C-cluster after removing S and R clusters and estimated waveform of C cluster, until there is a converged C latency and waveform simultaneously. Thus, single-trial latency and amplitude of C cluster is available by applying RIDE, making the analysis of ISV of ERP more reliable. The RIDE method has been successfully applied in several experiments (Ouyang et al., 2013, 2016(a), 2016(b), 2017). In my thesis, I will first justify the advancement of RIDE by applying it to experimental data to recover its smeared ERP amplitude by conventional analysis scheme (Chapter 3), then apply RIDE to a different dataset (Chapter 5) to extract and analysis the within-subject variability of C component latencies across experimental trials.

2.2.2 Structural Equation Modelling

As introduced above, Structural Equation Modelling (SEM) is used for studying latent variables which could not be directly measured but can be indirectly indicated by several related manifest (observed) variables with common variance. An example for latent and manifest variable could be human intelligence and scores of several intelligence-related tasks. There are two principle components of an SEM: *measurement model* which describes how *latent variables* are accounted for by observed variables, and *structural model* which assesses relationships among latent variables.

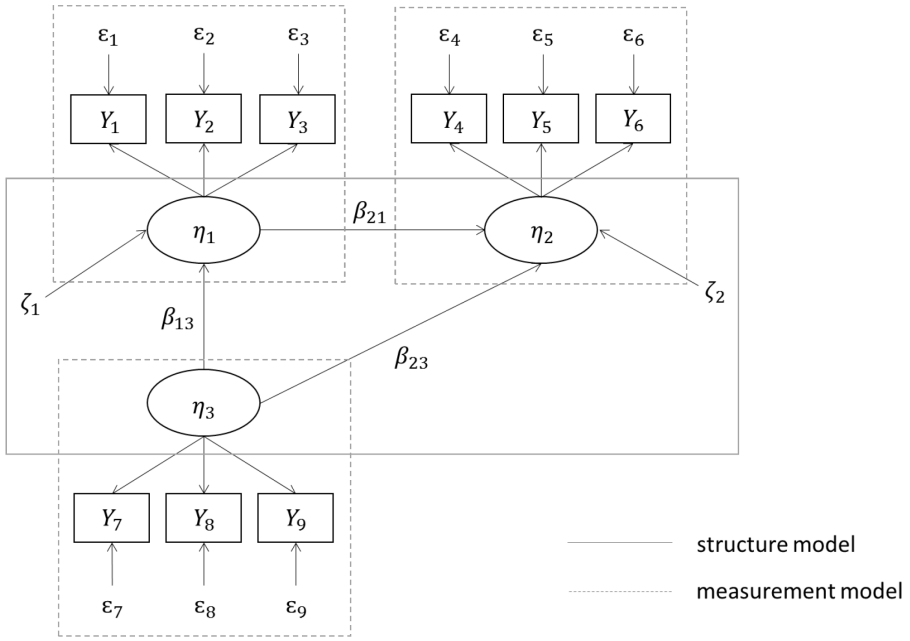

Figure 2-4. Schematic representation of Structural Equation Model. Y_i : manifest variables that can be directly measured; η_j : latent variables indicated by manifest variables; λ_{ij}: factor loading of η_j on Y_i. β : regression coefficients. ε_i : residuals.

The measurement model shown in Figure 2-4 could be described in the following equation:

$$Y_1 = \alpha_1 + \lambda_{11}\eta_1 + \varepsilon_1 \quad (1)$$

$$Y_2 = \alpha_2 + \lambda_{21}\eta_1 + \varepsilon_2 \quad (2)$$

$$Y_3 = \alpha_3 + \lambda_{31}\eta_1 + \varepsilon_3 \quad (3)$$

... …

$$Y_9 = \alpha_9 + \lambda_{93}\eta_3 + \varepsilon_9 \quad (9)$$

The structural model of the relationship among latent variables could be described as:

$$\eta_1 = a_1 + \beta_{13}\eta_3 + \zeta_1 \quad (10)$$

$$\eta_2 = a_2 + \beta_{21}\eta_1 + \beta_{23}\eta_3 + \zeta_1 \quad (11)$$

In the model, Y_i represented in the squares are manifest/observed variables, which could be measured directly. η_j represented in the circles are latent variables. The issue of model

identification is to estimate all the unknown model parameters with population covariance and mean that were already known from the manifest variables Y_i. Based on the above model expression, the population covariance matrix of the observed variable can be written as function of the unknown model parameters. For example, from equation (1) we can get

$$\mathrm{Var}(Y_1) = \lambda_{11}{}^2 Var(\eta_1) + Var(\varepsilon_1) \qquad (12)$$

From equation (1) and (2) we get

$$cov(Y_1, Y_2) = \lambda_{11} \cdot \lambda_{21} \cdot Var(\eta_1) \qquad (13)$$

The left side of the above two equations are the components of covariance matrix of the observed variable Y_i, while the right side is the component of expected population covariance matrix under the proposed model that is unknown and needs to be estimated. From equation (1) – (9) we can also write out the mean values (expectation) of the observed variable Y_i . For example, equation (1) gives the following equation

$$E(Y_1) = \alpha_1 + E(\eta_1)$$

and same for equation (2) – (9). The left side of the above equation represents the mean (expectation) of observed variable Y_i, and right side represents the unknown parameters to be estimated. When the number of measurable information (expectation or covariance matrix of observed variable Y_i) exceeds the number of unknown parameters, the model can be identified, which means that all model parameters can be estimated. Then, basing on the above information, estimation of the unknown model parameters is based on the minimization of deviation between the observed and model implied covariance matrix. Various methods based on different definition of deviation, as well as different assumptions can be used for model estimation. The most commonly used method is Maximum-Likelihood Estimation.

In a structural equation model, the most important parameter of interest is the factor loadings λ and the regression coefficients β. The former describes how well the observed variables can be explained by the hypothetical latent variable, and the latter describes the relationship between the latent variables. Before modeling one should have a hypothesized model, which is used to fit available measurements. If the model fit meets certain criteria, then the hypothesized model is acceptable. If the model fitting is not satisfying, one may add or reduce model parameters such as factor indicator, regression path or residuals, basing on the

significance of parameter estimation. Model fitting evaluation is usually based on the following criteria: χ^2 value, root mean square error of approximation (RMSEA < .08), comparative fit index (CFI > .95) and the standardized root mean square residual (SRMR< .08).

2.2.3 Multiscale Entropy – indexing brain signal complexity

As introduced in Chapter 2, multiscale entropy (MSE) is a widely used measure of complexity in time series. The MSE algorithm includes the following steps:

Step 1: Apply a "coarse-graining" procedure to the time series. For one time series, data points should be averaged with scale factors τ into coarse time series, so that all the point within the time window of length τ were averaged and composed the coarse-grained time series. The process can be described with the following equation:

$$y_j^\tau = 1/\tau \sum_{i=(j-1)\tau+1}^{j\tau} d_i$$

where y_j^τ refers to the j^{th} element for scale τ coarse time series. d_i represents for the i^{th} element of the initial time series.

Step 2: For the coarse-grained time series data obtained from step 1 under each scale factor, calculate the Sample Entropy, which is the negative logarithm of the pattern predictability of data length m. For example, if m is set as 2, then the pattern predictability is calculated as the total number that 2 data point sequence pattern match divided by total number that the third data point sequence pattern still match.

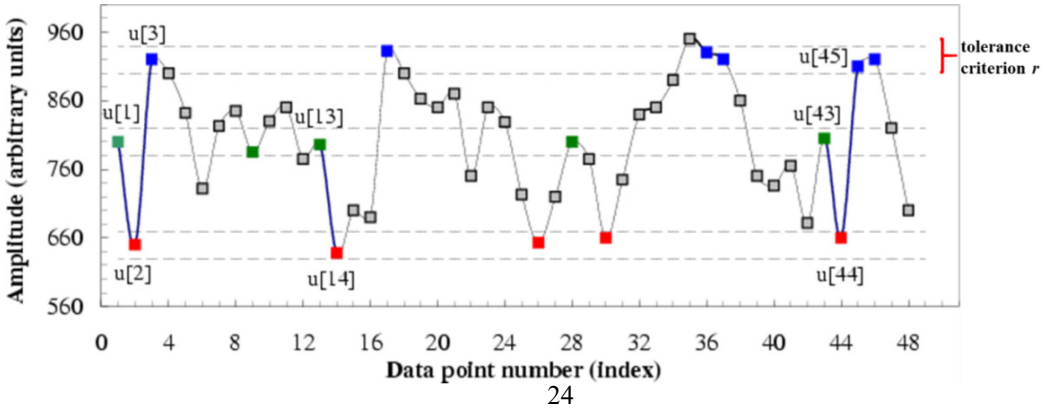

Figure 2-5. Schematic illustration of pattern match searching for calculating Sample Entropy. Data points of same color represent data points that match each other within tolerance criterion *r*. (Adapted from https://physionet.org).

Figure 2-5 gave illustration of the pattern predictability when m = 2. In Figure 2-5, u[1], u[2] and u[3] are the first pattern template with 3 data points, while u[1] and u[2] are the related pattern templates with 2 data points. Then there were two patterns with 2 data points that match u[1] and u[2]: u[13] and u[14], as well as u[43] and u[44]; and there was one pattern matching in the first 3-data point template: u[43], u[44] and u[45]. The searching of corresponding data points matching the pattern template was accomplished by finding all the data points whose amplitude is within the amplitude of u[1] $\pm r$, u[2] $\pm r$ and u[3] $\pm r$. In Figure 2-5, the total number of pattern matches with m +1 data point was 1, and the total number of pattern match with m data points was 2. Therefore, the predictability $p(m) = \frac{1}{2}$. Then Sample Entropy could be described with the following equation:

$$SampEn(m) = -\ln p(m)$$

After calculating the Sample Entropy for all the coarse-grained times series, MSE is plotted as a curve with scale factor τ on x-axis and Sample Entropy on y-axis.

Latent construct of MSE

Since my doctoral study is designed in the framework of individual difference, the application of MSE measurement in my study is largely addressed by means of Structural Equation Modelling. Following the study by my colleagues Kaur et al. (2019), who investigated individual differences in MSE as a latent construct under different brain states, the way of implementing SEM on MSE measurement is to apply the measurement model to construct a latent MSE variable, which is indicated by MSE estimations based on EEG segments with the same length from the whole EEG recording (Figure 2-6). In my study, the choice of EEG segment length for MSE estimation is decided by a trade-off between reliability of MSE estimation and limited sample size. In the next session, I will analyze the relationship between reliability of MSE estimation, length of EEG recording and sample size of my study so as to provide criteria for the choice of data length used for MSE estimation.

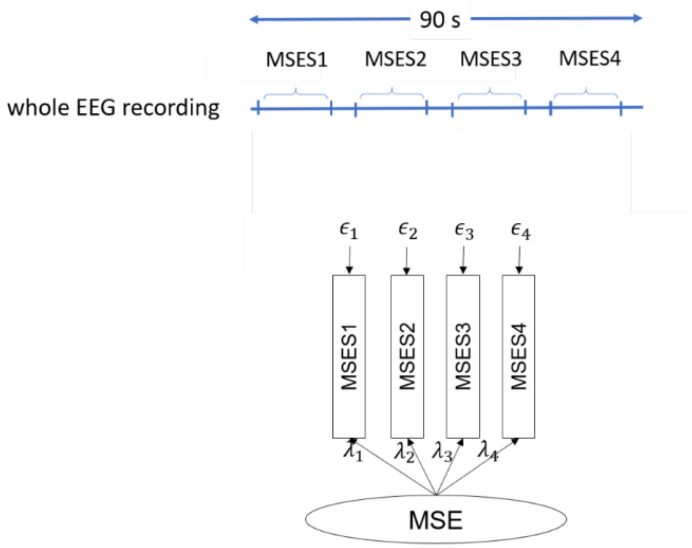

Figure 2-6. Schematic representation of measurement model for MSE. MSES1-MSES4 are MSE indicators calculated using segments of the whole EEG recording.

Reliability of MSE estimation

It is a consensus that the estimation of MSE should be based on sufficiently long time series, otherwise the high-scale estimation would have large variance because the coarse-graining process shortens the time series. Meanwhile, requirement for sufficiently long EEG time series will exclude some participants whose EEG recording is too short after the removal of segments with strong artifacts after pre-processing. In our case, we want to have EEG segments for MSE calculation that are as long as possible. Meanwhile, not too many samples should be discarded because we want to keep as much participants as possible for further analysis with enough statistical power.

The reliability measurement I used for MSE estimation is called the Composite Reliability, or usually referred to as McDonald's coefficient. It is widely used for evaluating the internal consistency of a measure by calculating the proportion of true score variance and covariance in the indicators of the measure among the sum of the variance, as is described in the following equation:

$$CR = \frac{(\sum \lambda_i)^2}{(\sum \lambda_i)^2 + (\sum \epsilon_i)}$$

Whereby, λ is the standardized factor loading of the i_{th} item on the latent construct; ϵ is the error variance of the i_{th} item estimated as

$$\epsilon_i = 1 - \lambda_i^2$$

Following this calculation scheme, I calculated the reliability of MSE estimations from EEG time series with length 10s (2500 data point), 12s (3000 data point), 16s (4000 data points), 18s (4500 data points) and 20s (5000 data points). As it was introduced in 2.1, there were two available datasets (Sample 3 and Sample 5) with resting state EEG recordings to be used in my doctoral study in combination. The sample sizes with data lengths 10s, 12s, 16s, 18s and 20s of the total participants of the combined dataset were: 250, 238, 221, 192 and 146.

Before starting to analyze, I also investigated the reliabilities of MSE estimation with different data length from scale 1-20, so as to provide reference in choosing of data length. Taking Fz and Pz as two representative channels, results are given in Figure 2-7.

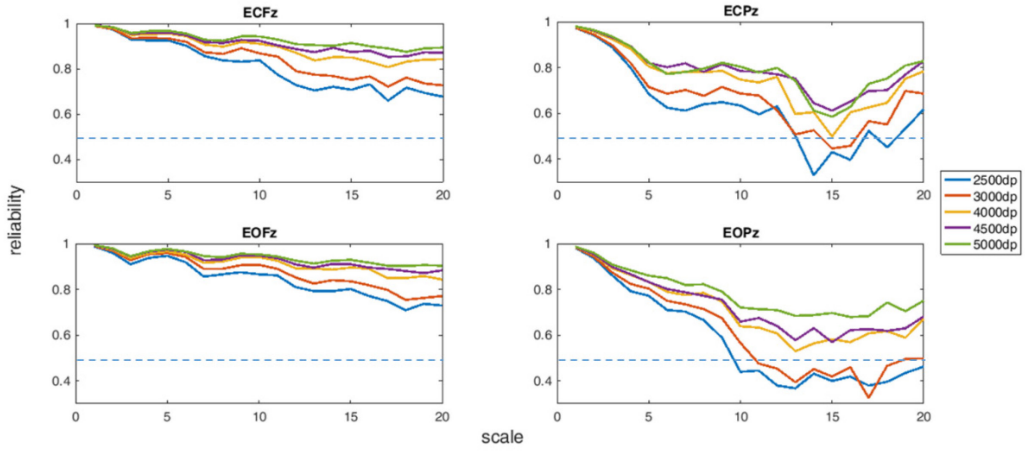

Figure 2-7. Reliability of MSE estimated with different data points (data length) for Fz and Pz channel under closed and open eyes resting state condition. EC – eyes closed condition; EO – eyes open condition.

According to Figure 2-7, the reliability is acceptable (above .5) for scale 1-20 when data length is above 4000 data points. For scale 1-10, the reliability is acceptable even when data length has only 2500 data points. Also, it is interesting that Pz channel has much less reliable MSE estimation than Fz. But this difference was not discussed in detail in the current thesis.

3. Neural Correlates of Resource Allocation During Emotional Speech Processing among Individuals with Different Levels of Autistic Traits -- Validation of Applicability of RIDE Method in Autistic Research

The main goal of my thesis is to study the relationship between APOE polymorphism, brain signal complexity and cognitive ability. An important methodological improvement to achieve this goal is the application of RIDE method to obtain latency variability information in single trial ERPs. Therefore, before starting going into the main topic, I first conduct a study to validate the applicability and superiority of RIDE method. The analysis is based on a study sample collected by our collaborator Dr. Lui from the Department of Education Studies of Hong Kong Baptist University, for the aim of autistic study. Background in autism and details of the study sample will be introduced in this Chapter.

Autism Spectrum Disorder (ASD) characterizes individuals with impaired social communication and restricted behaviors (American Psychiatric Association, 2013). In previous studies, autistic traits have been shown to be spectrum across individuals with a range of age (Baron-Cohen, et al., 2001; Ruzich et al., 2015). In previous studies, the diagnosis of ASD were largely restricted to the behavioral criteria defined by various diagnostic manuals. Recent development in neuroimaging technologies (e.g., EEG) that bring up the biological basis of autism have widened the view of autistic diagnosis, so that the psychophysiological alteration may also be detected among ASD individuals.

There are consistent findings showing that ASD individuals have declined facial emotion recognition (Masefsky and Oswald, 2007, Faja et al. (2016)) as well as emotional speech processing (Lerner, McPartland & Morris, 2013). Since speech is an important human communication approach, the impaired speech emotion recognition ability might lead to mismatch with facial emotion. Identification of speech emotions requires one to combine the semantic meaning of the word and the emotional prosody expressed during word communication. The widely known ERP component related to this semantic incongruity is N400. When there is mismatch between semantic meaning and emotional prosody, the amplitude of N400 will become larger (Kutas & Federmeier, 2011).

Empathy is another important social cognitive function, which characterizes people's ability in recognizing the feelings of other people. Therefore, empathy is an essential competence to enhance the social communication among people. Similar to AQ, the Empathy Quotient (EQ) has also been proposed as a valid measurement of empathy (Baron-Cohen and Wheelwright, 2004). Previous study has shown that high autistic level is associated with impaired empathizing ability, and the predictability of EQ on AQ has been shown to be significant (Wheelwright et al., 2006). Therefore, it is meaningful to study EQ as well in autistic study.

This study is based on a previous study by Lui et al. (2018), where difference in processing semantic congruity during emotional speech between high and low male Autistic Quotient (AQ) persons was found on both behavioral and ERP levels. The difference was pronounced under happy (positive) condition rather than sad (negative) condition. However, we hypothesized that weaker difference could be induced by stronger latency variability of the N400 components in single trials in the sad condition, and through decomposing average ERP, the difference could be pronounced under both happy and sad experimental conditions. By applying RIDE method on the study sample with same male participants with Lui et al. (2018) and added female participants, we aim to increase the distinguishability of N400 congruent-incongruent ERP amplitude difference between low and high autistic levels. Basing on our finding, we want to further investigate whether the N400 amplitude difference between congruent and incongruent emotional processing condition could be developed as a biomarker for characterizing AQ level. Furthermore, it is also of interest whether this biomarker could be valid for the prediction of EQ as well.

Study sample

The focus of this current study is methodological advancement (application of RIDE) based on the previous study by Lui et al (2018). Therefore, the sample and ERP recording were partly overlapping with the sample applied in that study.

Participants: The dataset included 68 Cantonese speakers who completed the Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001) online questionnaire. The age of the sample ranged from 18-30 years, 42 of them were male. The participants were categorized as low AQ (AQ <18), high AQ (AQ > 25) and mid AQ (18 < AQ < 25). In the study by Lui et al. (2018), only male participants grouped as low and high AQ were analyzed. The current study

further included female participants and mid AQ group participants, therefore enabled individual difference analysis beyond merely group comparison.

Experimental stimuli: The stimuli used for ERP experimental were disyllabic Cantonese words rated according to familiarity and emotional valence in daily life usage by non-participants with similar age. 60 of the words were positive in semantic meaning and 60 were negative. Sound stimuli were produced with either happy or sad prosody. Each word was presented twice with both happy and sad prosody. Therefore, 240 stimuli were presented to each participant, giving 240 experimental trials with 4 different experimental conditions: 60 happily spoken positive words (congruent), 60 happily spoken negative words (incongruent), 60 sadly spoken positive (incongruent) words, and 60 sadly spoken negative words (congruent).

The 4 different experimental conditions could be grouped as congruent condition, which contains happily spoken positive word and sadly spoken negative word, as well as incongruent condition, which contains happily spoken negative words and sadly spoken positive words. Sound intensity levels of congruous and incongruous stimuli were compared and no significant difference was detected (p = .21). The mean durations of positive and negative word did not differ significantly (p = 1.00), but there was significant difference between mean durations of happily and sadly spoken words ($p < .01$).

Data processing and statistical analysis: In the previous study by Lui et al. (2018), ERP comparison was based on original ERP recordings after typical EEG preprocessing, where single trials were automatically averaged, thus smeared out between-trial variabilities as described in Chapter 2. In this current study, basing on the 60 trails in each of the four conditions of each participant, RIDE method as described in Chapter 2 was applied to the preprocessed EEG signals with the RIDE toolbox (Ouyang et al., 2015(a); 2015(b)), so as to construct new ERP with a non-smeared central-processing (N400) component. Therefore, each individual has four reconstructed ERP curves with four different conditions: positive congruent condition, positive incongruent condition, negative congruent condition and negative incongruent condition. Following Lui et al. (2018), nine central-parietal electrodes (Cz, C1, C2, C3, C4, CP1, CP2, CP3 and CP4) were included to represent the central-parietal ROI, because Kutas & Federmeier (2000) showed that semantic memory, which is related to N400 ERP component, is maximized at central-parietal region.

The ERP difference of both positive and negative condition of each individual was computed as incongruous ERP subtracting congruous ERP. The difference ERP was standardized for each individual to take account into the individual difference in ERP. The standardization was applied as follow:

$$ERP\ difference = \frac{incongruous\ ERP - congruous\ ERP}{congruous\ ERP}$$

Pearson correlation between ERP difference and AQ and EQ scores was computed for different experimental conditions (positive vs. negative) and ROIs (frontal and central-parietal).

ERP amplitude difference between congruous and incongruous condition

According to previous study (Lui et al., 2018), significant difference in amplitude of N400 was detected when comparing the ERP recording under congruous and incongruous stimulus (see Fig. 3-1). Specifically, the significant difference was detected among low AQ participants, rather than high AQ participants. In other words, those participants with higher autistic levels were less capable to differentiate neural resource allocated to emotional processing.

This ERP founding has clinical impact in the way that it provides possibility to evaluate the autistic level through ERP measurement, which is novel on the autistic diagnosis level. However, in the work by Lui et al. (2018), this difference in ERP distinction between low and high AQ was only detected under happy condition. We aim to seek possibility to improve the sensitivity of this measure as a more valid biomarker of autistic level which could be generalized to both positive

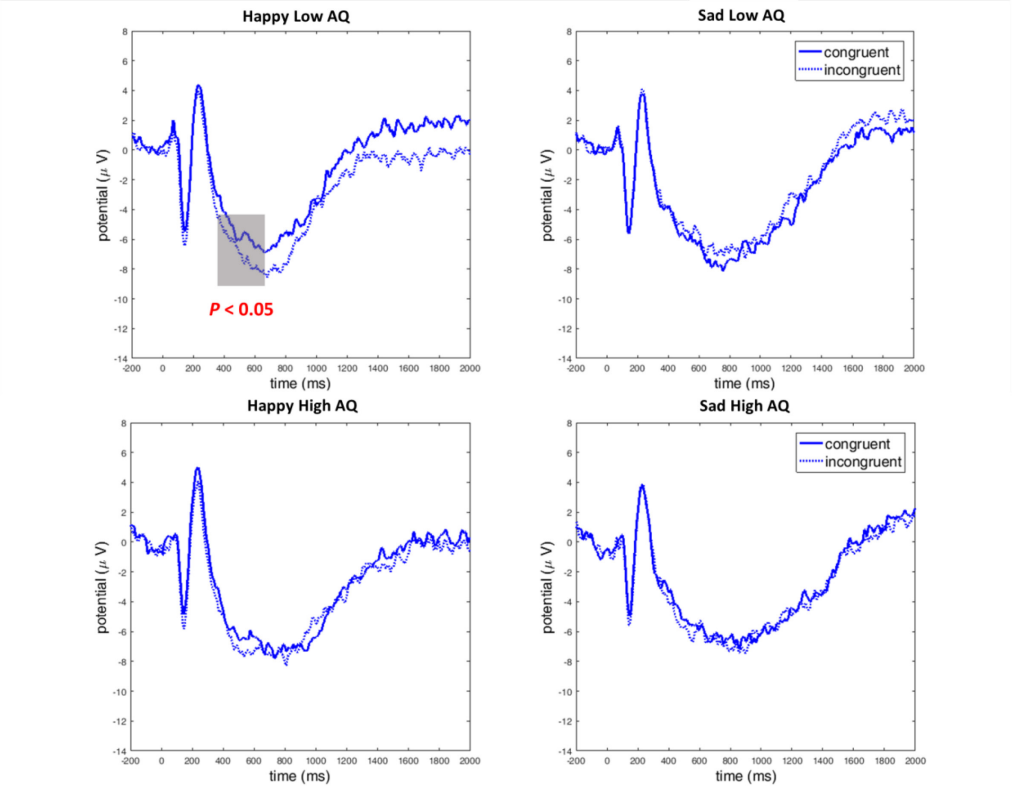

Figure 3-1. Comparison of conventional ERP amplitude of Cz electrode between congruous and incongruous stimulus under happy and sad condition. Upper panel (Recalculated from data applied by Lui et al., 2018)

and negative experimental conditions. Previous work showed that difference in conventional ERP includes contribution from latency variability of the component of interest across single trials, and in some cases, insignificant differences in ERP could be induced by different degree of latency variability, even though the underlying components could be actually significantly different (Ouyang et al. 2016). Figure 3-2 showed that especially for low AQ participants, the within-person RT variability (calculated as standard deviations of each subject) of the sample applied in the current study is larger under sad condition (Row 3 and Row 4) than happy condition (Row 1 and Row 2). However, the incongruent condition does not seem to have larger RT variance than congruent condition. Therefore, it is possible that by applying RIDE, the amplitude of both congruent and incongruent sad ERP will be enlarged, but it's not clear whether the difference between incongruent and congruent sad ERP will also be enlarged after removing the smearing caused by latency jitter.

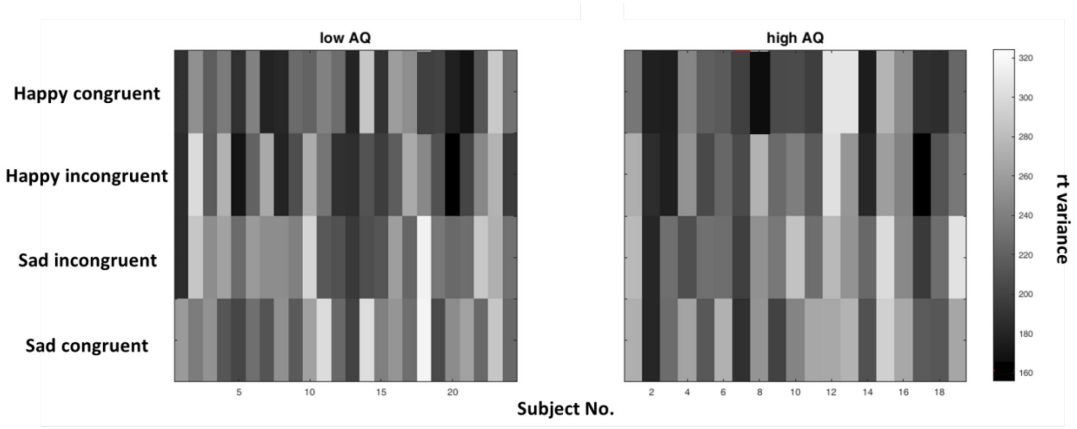

Figure 3-2. Comparisons of variance of RT between experimental conditions for each participant. Different rows represent four experimental conditions. Each grid in the figure represents the magnitude of RT variance across trials of each participants.

Increased ERP amplitude difference between congruous and incongruous condition after applying RIDE

As is explained in the introduction of RIDE method, original ERP recording is averaged from multiple single trials, therefore smearing out the amplitude of each trial because of stimulus-locked ERP latency jittering (Ouyang et al., 2016). The rational to fix this problem is reconstructing new ERP which is averaged across C-latency-locked single trials. Basing on the current sample which also includes female participants, Figure 3-3 and 3-4 gives a comparison between RIDE reconstructed ERP and conventional ERP recording on Cz channel as a representative channel under happy condition. It could be visually detected from Figure 3-3 that after applying RIDE, the ERP difference between congruous and incongruous condition was enlarged under both happy and sad condition. Specifically, under sad condition, the incongruent ERP amplitude was firstly smaller than congruent ERP amplitude before around 900 ms, then became larger than congruent ERP amplitude after 900 ms. Therefore, under both conditions, the RIDE reconstruction process increased the ERP difference between congruous and incongruous condition among low AQ participants. However, for both conditions, the ERP amplitude difference was not significant either before or after the application of RIDE. Comparing to result by Lui et al. (2018) where the ERP difference was already significant under happy condition, the current dataset with female participant added somehow smeared the ERP difference. Among high AQ participants, as is shown in Figure 3-4, the ERP difference was not clearly enlarged by RIDE for both happy and sad condition.

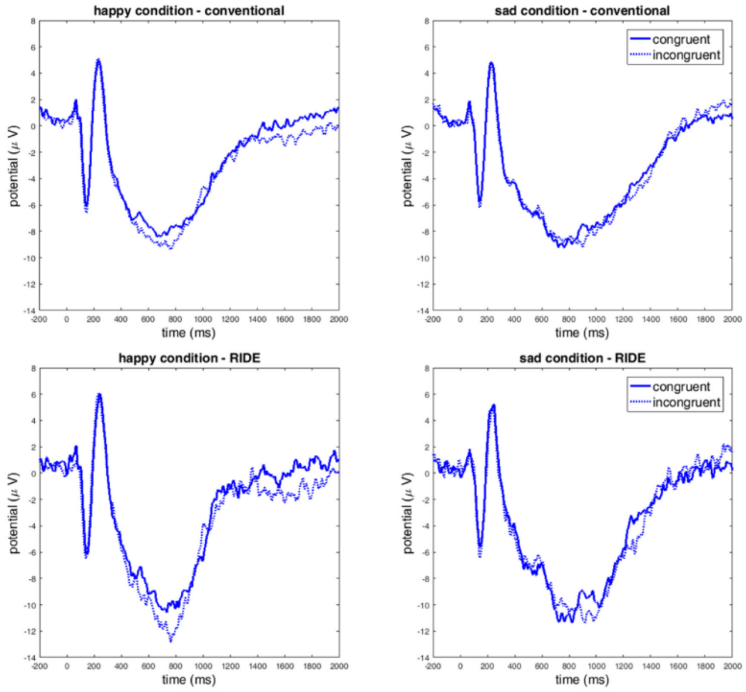

Figure 3-3. Comparison of conventional ERP and RIDE reconstructed ERP of low AQ participants under happy and sad conditions. ERP wave was calculated as grand ERP by averaging across experimental trails and individuals within each group.

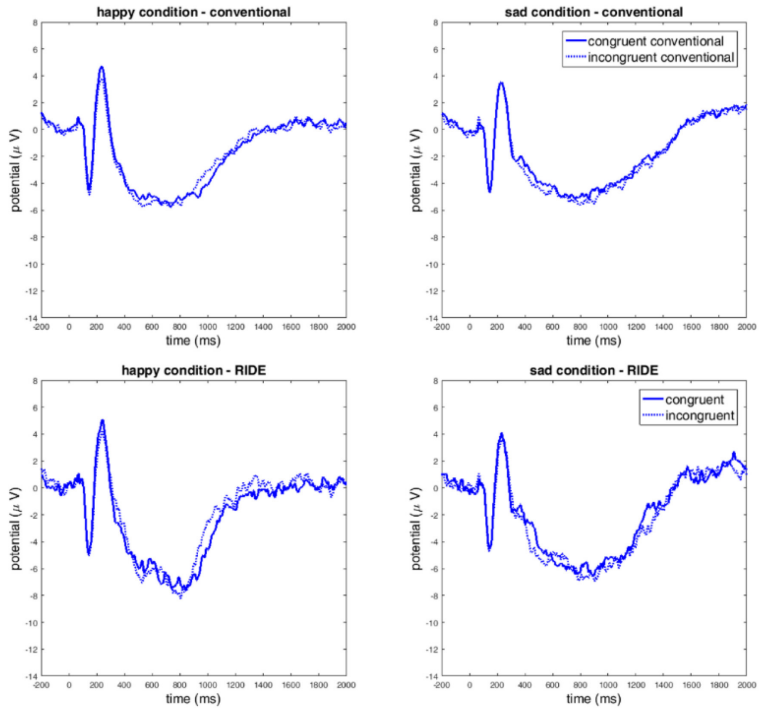

Figure 3-4. Comparison of conventional ERP and RIDE reconstructed ERP of high AQ participants under happy and sad conditions. ERP wave was calculated as grand ERP by averaging across experimental trails and individuals within each group.

Even though failing to detect significant group difference of congruent and incongruent ERP amplitude, the dataset applied in the current study was superior in the way that it includes a spectrum of autistic scores, rather than simply low and high AQ groups applied by Lui et al. (2018). Moreover, the sample size was much larger with female participants added (68 participants in total). The AQ score of the whole sample ranged from 7 to 36, which enabled the investigation on the correlation between ERP congruous-incongruous differences and AQ scores across the participants. According to Figure 3-3 and 3-4 we further hypothesize that the ERP difference would be differed across the autistic spectrum. After applying RIDE method on the original ERP recording, the incongruous-congruous ERP difference would be a sensitive enough biomarker of AQ score and could be generalized to both positive and negative semantic conditions.

According to Lui et al. (2018), the significant ERP congruous-incongruous difference in conventional ERP was detected in the time window 50-200 ms (for N200 component) and 350-600 ms (for N400 component). In our case, the N400 difference was hypothesized to characterize AQ score. However, the relevant time window may be shifted after the application of RIDE and may not be the exactly the same window to test whether the N400 difference is significantly correlated with AQ score. According to Figure 3-3 and 3-4, we could visually inspect that the N400 component in sad condition occurred later than happy condition, indicating that more stimulus evaluation was needed for sad condition as compared with happy condition. Therefore, we choose 350 - 600 ms as time window applied under happy condition and 400 – 650 ms as time window applied under sad condition, where the sad condition had 50 ms time delay of N400 occurrence.

Basing on the above time windows the ERP difference was calculated and correlated to AQ score, and the result was displayed in Figure 3-5. The ERP difference score was calculated as standardized ERP difference averaged across the 9 channels at central ROI. Since EQ score has been shown to be negatively related with AQ score, we further correlated the ERP difference to EQ score, so as to assess whether AQ and EQ could be simultaneously predicted by the ERP N400 component difference, as displayed in Figure 3-6.

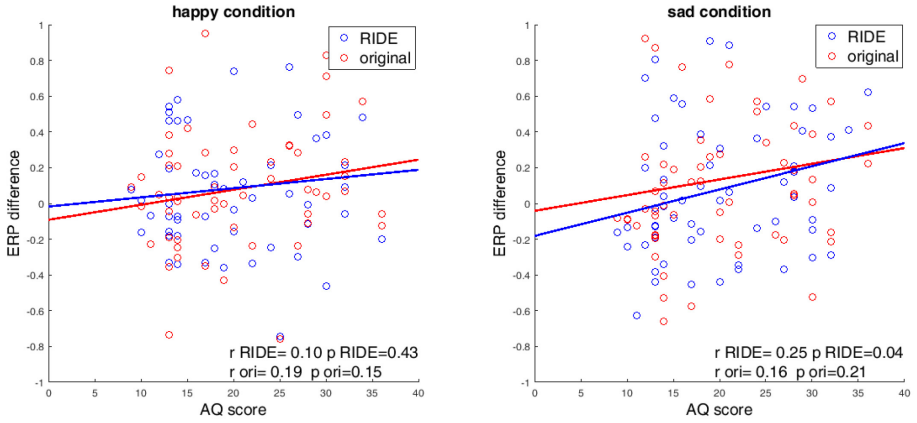

Figure 3-5. Correlation between ERP difference (properly rescaled by ERP amplitude) and AQ score across participants under time windows: 350 – 600 ms for happy condition and 400 – 650 ms under sad condition. r RIDE: correlation coefficient of RIDE reconstructed ERP difference and AQ score; p RIDE: p-value of RIDE reconstructed ERP difference and AQ score correlation; r ori: correlation coefficient of original ERP difference and AQ score; p ori: p-value of original ERP difference and AQ score correlation.

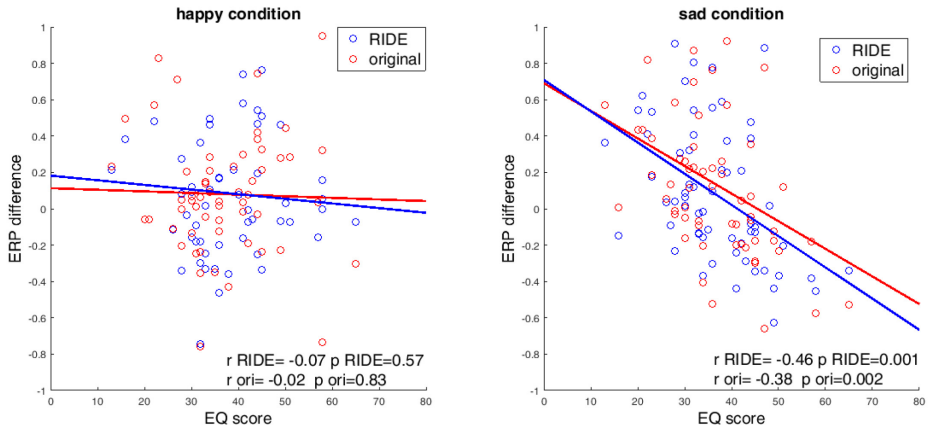

Figure 3-6. ERP difference correlation with EQ score across participants under specifically chosen time windows: 350 – 600 ms for happy condition and 400 – 650 ms under sad condition. For abbreviation see Figure 3-5.

As is indicated by Figure 3-5 and 3-6, after RIDE reconstruction, the correlation between ERP difference with AQ and EQ score was largely improved. Under sad condition, the improvement was more consistent for both AQ and EQ correlation. For the correlation between ERP difference score and AQ score under sad condition, the application of RIDE has especially enlarged the correlation, turning the insignificant correlation into significant correlation. Under happy condition, the increase of correlation only exists for EQ score,

though not significant even after RIDE reconstruction. The direction of correlation was positive for AQ and ERP difference and negative for EQ and ERP difference, because AQ and EQ are two measures that basically anti-correlated. Very interestingly, as could be viewed from the right panel of Figure 3-5 and 3-6, for high AQ participants under sad condition, the ERP difference was also greater than zero. This means that unlike how we hypothesized before, high AQ participants are also sensitive to the incongruent semantic-prosody valence beyond the congruent condition. Due to the sexual difference in dataset, this conclusion was not claimed by Lui et al. (2018).

Discussion

ERP analysis was performed on the difference in N400 amplitude of congruous and incongruous semantic conditions with a novel ERP decomposition method (RIDE). The analysis was based on a previous study (Lui et al., 2018) which investigated the ability to distinguish incongruous and congruous prosody on vocal semantic expression of participants with low and high autistic levels. Lui et al. (2018) concluded that higher autistic level was associated with decreased ability in distinguishing emotional vocal stimuli with different semantic meaning under positive condition, rather than negative. Using the dataset including the same male participants and added female participants as well as middle-level AQ male and female participants with RIDE ERP decomposition method, this current study suggested that the difference between incongruent and congruent ERP could be a predictor of AQ and EQ score and the predictability is largely improved by RIDE. Therefore, we could possibly develop the ERP N400 difference in congruous and incongruous condition as a biomarker of autistic level.

Choosing of time window used for N400 difference analysis

In this current study, the chosen of happy condition time window used for N400 difference was following Lui et al. (2018). After a time window searching process on every 50ms of the whole recording process, they decided the final time window so that there are more than three consecutive 50ms time window with significant difference between congruous and incongruous ERP, so that the problem of inflated type I error caused by multiple correlation could be avoided. Therefore, the length of the final time window should be longer than 150ms. Following their decision, we decided to chose 350-600 as final time window for the detection of AQ score with ERP difference enlarged by the RIDE method. We made this

decision because our hypothesis that the AQ level could be predicted by the ERP difference was arbitral driven from the conclusion that the ERP difference was differed for low and high AQ levels by Lui et al., (2018). However, further investigation in detail whether there's true correlation exists could be carried out.

Novel founding of RIDE beyond conventional ERP analysis

One goal of the current study was to increase the distinction in neural allocation under congruous and incongruous prosody-semantic speech expressions among low AQ persons. As compared with conventional ERP analysis, RIDE plays role in deeper mining of ERP information and therefore overcame the ambiguity of conventional ERP and recovered more of neural processing related brain function (Ouyang et al., 2013). Figure 3-2 and 3-3 revealed that the application of RIDE gave following information that was not uncovered through conventional ERP analysis: 1) The ERP amplitude incongruous and congruous difference was enhanced. 2) Under sad rather than happy condition, the incongruous ERP had smaller peak amplitude before the time 900 ms as compared with congruous among low AQ person. 3) The difference becomes positive for high AQ persons, and there is a positive correlation with AQ level. Specifically, the application of RIDE contributed to discover the underlying ERP difference at all AQ levels, which consistently change with the AQ score.

ERP N400 difference under different condition among low and high AQ people

N400 component was related with the semantic incongruity during processing of language (Hahne et al., 2002). This suggested that as compared with congruous condition, the incongruence between semantic and prosody expression may induce altered N400 amplitude for people with normal autistic level. Lui et al. (2018) suggested reduction in this sensitivity among high AQ people. The current study renewed the direction of incongruous peak amplitude change, that under negative condition, the amplitude may become smaller than congruous condition for low AQ persons. However, this opposite direction of amplitude difference is not well understood. Furthermore, as compared with Lui et al. (2018) with male-only dataset (Figure 3-1), the current study discovered that adding female participant enlarged the incongruous-congruous difference at the time window of 400 ms – 650 ms among high AQ participants, so that the ERP difference could be more sensitive to the change of AQ score. Besides the amplitude enlargement of RIDE method, the addition of female participants may play an important role in increasing the amplitude difference, that high AQ

females, even though not so sensitive to incongruent semantic-prosody valence under positive condition, may be sensitive to that under sad condition as compared with males.

Limitation of the current study

In the work by Lui et al. (2018), results were based on male participants. However, the current study also included female participants. Therefore, the results of ERP difference from the two studies could not be directly compared. In fact, gender difference has been shown to be an important factor in the study of emotional speech processing (Schirmer et al., 2006). Therefore, without adding gender as a potential interactor, the contribution of RIDE in adding the sensitivity of ERP difference to AQ score might be confounded. Further study with enlarged sample size acquired at all autistic levels may consider the interact effect of gender on the ERP difference and its relationship with AQ score.

4. Brain Activity and Cognitive Performance of Young Adults under Genetic Risk for Alzheimer's Disease

As introduced in Chapter 2, APOE ε4 allele is widely studied for its risk-increasing impact on Alzheimer Disease (AD) in human later life. The abnormality of APOE ε4 carriers is embodied at both psychophysiological and behavioral level. However, whether the abnormality is already detectable during young adulthood, when AD related-cognitive decline is not yet visible, is still largely debated. In this Chapter, I will present work investigating APOE genetic difference in MSE and working memory/reasoning performance studied in young healthy adults. The aim of the study is not only to add knowledge on the current discussion on APOE ε4 genetic effect on brain activity and behavior, but also to investigate the possibility for early diagnosis of AD. Since several study samples were included and there is a gap to connect measurements from different samples, currently we performed separate analyses for the genetic associations with cognitive performance and brain activity. Future work may seek to integrate the analysis of relationship between APOE genotype and phenotype on both brain and behavior levels in suitable experiments.

In this Chapter, study results will be demonstrated in two separate sections: the first section (6.1) will present the APOE ε4 effect on MSE in resting state EEG recordings. Two datasets collected with the same procedure were jointly analyzed. The second section (6.2) is about APOE ε4 association with WMC and reasoning as facets of cognitive ability. The study includes separate analyses of 4 different samples, two of them overlapping with the study on the association between APOE ε4 and MSE reported in section 6.2).

4.1 Effect of APOE polymorphism on the Multiscale Entropy of closed and open eyes resting state in healthy young individual adults

The pathology of AD is characterized by deposition of beta amyloid-Aβ and the accumulation of tau protein across different brain regions (e.g., Braak & Braak, 1991), leading to disturbed cortical connections. Many studies have demonstrated the decreased nonlinear cortical coupling or cell-dynamic (Jeong et al., 2001; 2004) measured from these functional disconnections, which could result in abnormal complexity in brain signal measured by EEG. As introduced above in detail, MSE is a widely used measurement of signal complexity. The

distinguishability of MSE in AD and healthy controls has been validated in previous studies (e.g., Mizuno et al., 2010; Niu et al., 2018).

The APOE ε4 allele accounts for 70% of the risk for AD in later life and constitutes the most important genetic risk factor. However, how the APOE ε4 genetic expression induces high risk for AD is not very clearly understood. Since APOE plays an important role in balancing cholesterol metabolism (reviewed by Rsamussen, 2016) and APOE ε4 is detected in neurofibrillary tangles and Aβ, the main stream point believes that APOE ε4 may mediate phenotype on brain activity level in the AD development procedure.

In this work I investigated the MSE of EEG recordings from young healthy carriers and non-carriers of APOE ε4 allele, basing on the assumption that MSE of resting state EEG is differentiable between APOE ε4 carriers and non-carriers. Furthermore, the direction of the difference is assumed to be scale-dependent and condition-dependent. That is, the direction of difference may depend on low and high MSE temporal scales, as well as on whether measured under closed or open eyes condition. The conditional difference is of interest because brain state, as well as the strength and consistency of brain activity may be affected by closed and open eyess resting conditions (Van Dijk et al., 2010; Patriat et al., 2013). Therefore, the difference between MSE measured under eyes closed and eyes open condition may also indicate the brain dynamic transferring from wandering to focusing mind state (Kaur et al., 2019, under review). As a facet of brain property that might be related to cognitive ability, I also assumed that the MSE difference between eyes open and eyes closed resting state is different among young healthy APOE ε4carriers and non-carriers.

Study sample

The sample applied in the current study was the combination of study sample 3 and 5 introduced in Chapter 2. The two samples had overlapping EEG recordings under resting state open and closed eyes. Both closed and open eyes had 90s of EEG recording. As introduced in Chapter 2, the EEG recordings of each participants should be cleaned by eliminating dirty segments such as artifacts and abrupt jumps. In this current study, cleaned EEG time series with longer than 12000 data points (48 s) were remained. After removing those participants with no long enough EEG time series, the final sample had 224 participants (47.6% ε4 carriers) under closed eyes condition and 249 participants (46.8% ε4 carriers) under open eyes condition.

In this study, individual differences in MSE among young adults with different APOE genotype (APOE ε4 carrier vs non-carrier) was investigated. In order to apply Structural Equation Modeling, a 0-1 dummy variable was applied as a predictor for the latent variable of MSE. Participants were grouped as APOE ε4 carriers, coded as 0, and non-ε4 carriers coded as 1. With Structural Equation Modelling, we not only assessed the APOE ε4 association with scale- and electrode-specific MSE estimation, but also used MSE AUC (area under curve) value as a measurement which integrated MSE estimation across a scope of temporal scales, as well as using latent variables which integrated MSE across several electrodes within a region of interest.

Statistical Analysis

Two types of model branching from the SEM family was applied: higher-order latent variable model and latent difference score model.

Higher-order latent variable model:

In a high-order latent variable model, the latent factors are defined hierarchically. There is a higher-order latent variable, which is indicated by several sub-factors (Figure 4-1). Each sub-factor is further indicated by several observed indicators. When several of all the indicators (e.g., Y_1 to Y_3 out of all the nine indicators) had larger common variance as compared with the common variance among all the observed indicators, then these several indicators could be clustered into a sub-factor (e.g. η_1). Then the sub-factors could be further generalized into a higher order factor η, which account for the common variances among η_1 to η_3.

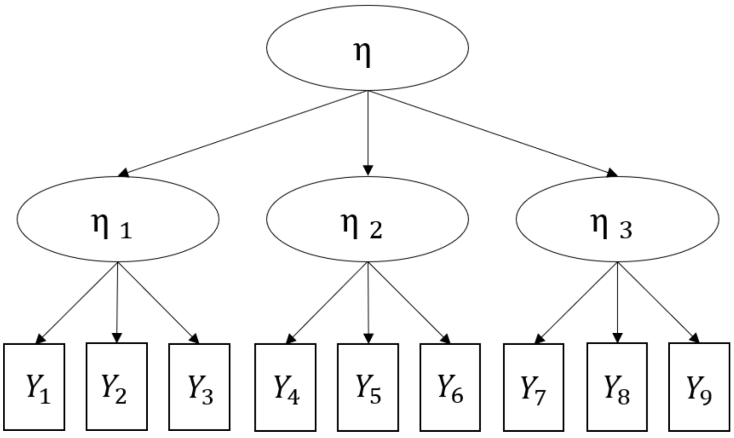

Figure 4-1. Schematic representation of higher order latent variable model. Y_1 to Y_9 are observed indicators. η_1 to η_3 are sub-factors which account for common variance among Y_1 to Y_3, Y_4 to Y_6 and Y_7 to Y_9. η is the higher order factor which account for common variance among η_1 to η_3.

Latent difference score model:

Latent difference score model is applied for evaluation of the difference between two latent variables (η_1 and η_2 in Figure 4-2). More specifically, the latent difference variable (η in Figure 4-2) could also have been indicated by the manifest difference (e.g. Y_4 subtracting Y_1 in Figure 4-2). However, the reliability of this measurement could be low, because the covariance construct of η is dependent on the correlation between Y_1 and Y_4. Furthermore, larger measurement error will be induced by this indicator (Little et al., 2006)

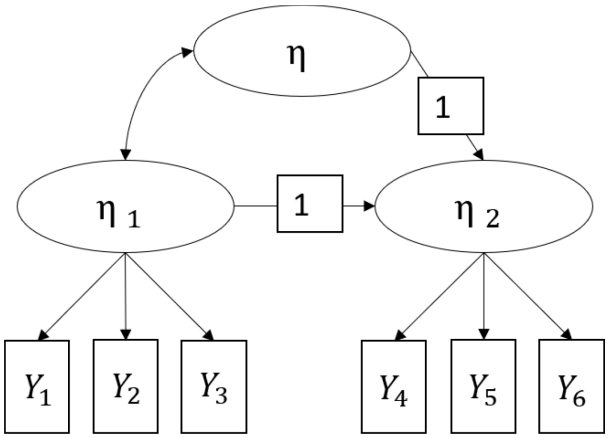

Figure 4-2. Schematic illustration of latent difference score model representing the difference η_2 subtracting η_1. Double ended arrow represents for the correlation between variables. Regression coefficients on η_2 are fixed to 1.

By fixing the regression coefficient as 1, η_2 could be represented as equation:

$$\eta_2 = 1 \cdot \eta + 1 \cdot \eta_1$$

So that η represents the difference between η_2 and η_1 (McArdle, 2009).

APOE ε4 effect on single-scale MSE

We started with assessment of APOE ε4 effect on single-scale MSE. For each electrode and each single scale, we applied the following SEM model as represented in Figure 4-3:

In this model, the latent variable of MSE was indicated by three MSE indicators each calculated from EEG segments with length of 16s (4000 data points), because with this date length the reliability of MSE estimation is satisfied for scale 1-20 (as explained in Figure 2-7). The standardized regression weights, which represent how much variance of the MSE latent variable could be accounted for by ε4/non-ε4 variable, were obtained for each MSE temporal scale and electrode. The standardized regression weight, referred to as effect size, was visualized in Figure 4-4.

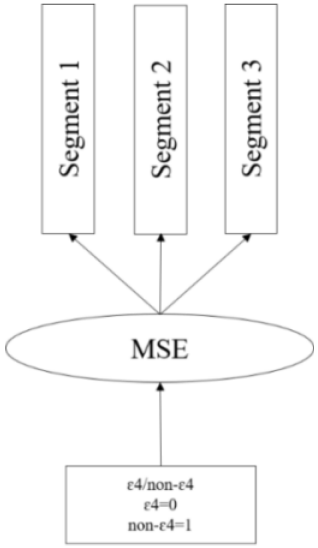

Figure 4-3. Schematic representing of structural equation model investigating the APOE ε4 association with MSE at each single scale

Figure 4-4 shows the topology plot of the effect size as described above. Since the APOE ε4 carrier vs non-carrier was coded as 0 vs. 1, blue color displayed on the figure corresponds to higher MSE and red color corresponds to lower MSE detected among the APOE ε4 carriers as compared with non-carriers. As demonstrated in the figure, under both eyes closed and eyes open conditions, at lower temporal scales (scale 1-4) MSE of APOE ε4 carriers was consistently higher across the scalp. When scale factor goes beyond four, the cross-scalp APOE ε4 effect pattern differed between resting state conditions and scale factors. Under eyes closed condition and scale factor below 10, MSE of APOE ε4 carriers was slightly higher as compared with non-carriers. For scale 11-20, there seemed to be no effect under eyes closed condition, indicating no difference in MSE between APOE ε4 carriers and non-carriers. Under eyes open condition, when scale factor was above four, there was an opposite APOE ε4 effect on MSE at frontal ROI. That is, MSE of APOE ε4 carriers is lower at frontal regions as

compared with non-carriers. At parietal region, the effects tended to be opposite to the frontal region, however not consistently detected from the topography.

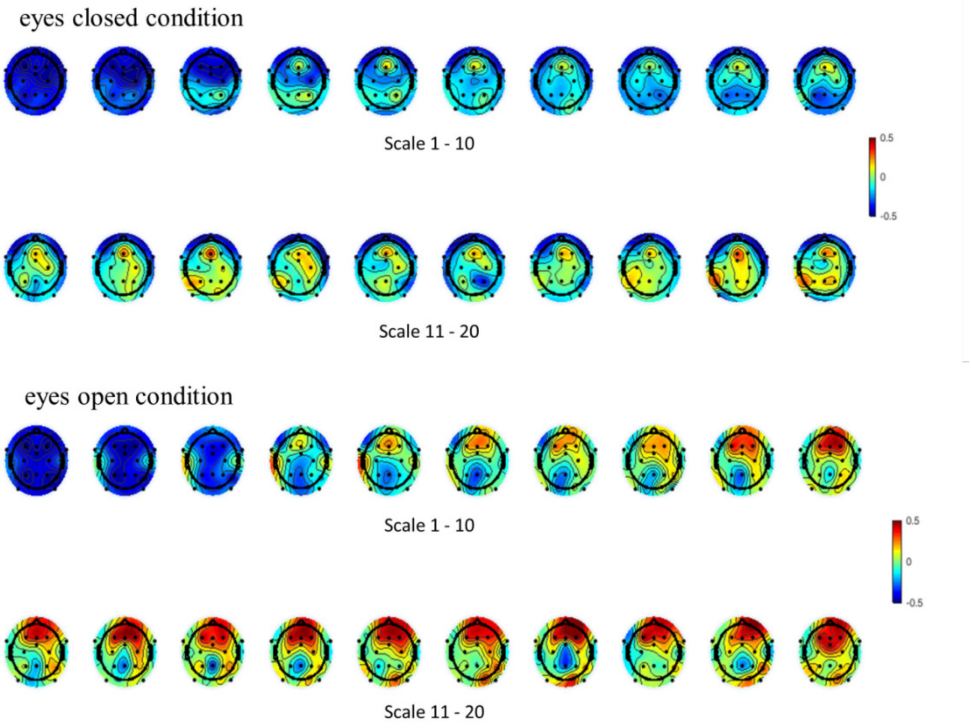

Figure 4-4. Topology of APOE ε4 effect size at scale 1-20. Blue color indicates larger MSE value among APOE ε4 carriers, red color indicates smaller MSE value among APOE ε4 carriers.

Figure 4-5 shows the group-wise and conditional comparison of MSE curves with respect to the scale factors. Comparison of the MSE curves of ε4 carriers under eyes closed condition, ε4 non-carriers under eyes closed condition, ε4 carriers under eyes open condition and ε4 non-carriers under eyes open condition were demonstrated.

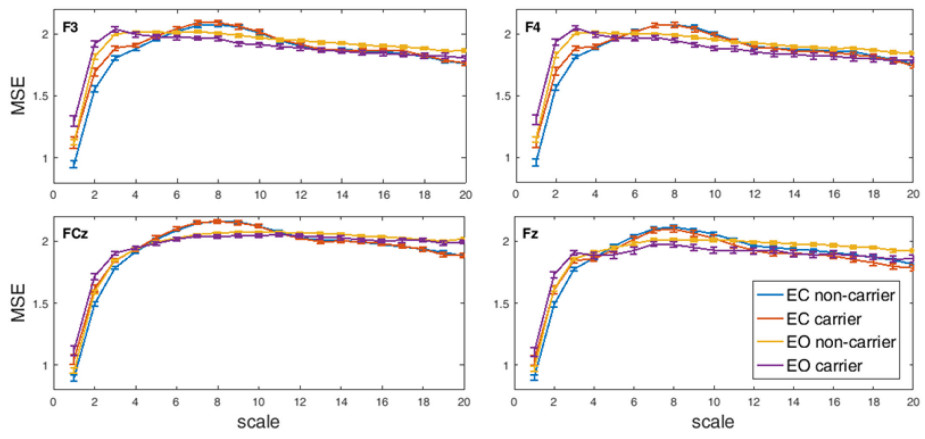

Figure 4-5. Line plot of grand mean MSE curve with standard error of all participants at F3, F4, FCz, and Fz electrodes.

The line plot showed consistent APOE ε4 effect which is differed between high and low scales. Furthermore, within eyes open condition there is a discernible crossing point at scale four for the ε4 carriers and non-carrier lines. Within eyes closed condition, the MSE curves for ε4 carriers and non-carriers were almost overlapping when scale factor was above five. On the other hand, within both ε4 carriers and non-carrier group, the patterns of MSE curves under eyes open and eyes closed condition were similar: firstly crossing at around scale four, then crossing at around scale 11.

APOE ε4 effect on MSE integrated across time scales and electrodes

One novelty of this study is to investigate the APOE ε4 association with MSE as a measurement integrated across temporal scales and EEG electrode sites. For scale-wise integration we applied the MSE Area Under Curve (AUC) score following Kaur et al. (2019, submitted). That is, to calculate the integration of MSE across certain scales. For electrode-wise integration, we applied a high-order construct of Structural Equation Modelling, where a higher-order latent variable of MSE would be indicated by electrode-specific MSE latent factors as described in Figure xx. According to the pattern of MSE curve as shown in Figure 4-5, scale 1-4 which displayed consistent pattern could be grouped together as low scale MSE. Similarly, scale 5-11 and scale 12-20 could be grouped together as medium scale and high scale MSE, so that MSE could be integrated as MSE AUC at low, medium and high temporal scales. The electrodes F3, F4, FCz and Fz, which are located at centro-frontal region and have representative MSE curve pattern could be spatially integrated as frontal region MSE. For parietal region, we choose P3, P4 and Pz electrodes accordingly so that the APOE ε4 association with MSE could be assessed and compared at these two regions.

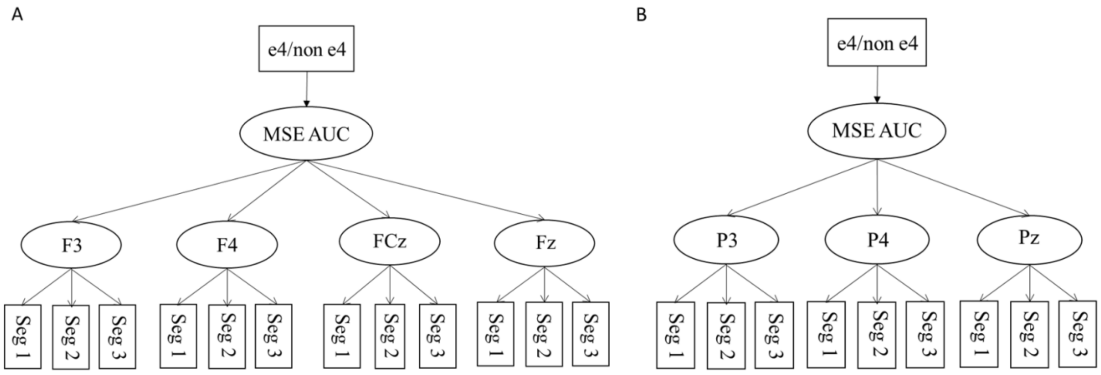

Figure 4-6. Structural equation modeling exploring APOE ε4 association with latent variable MSE AUC score at frontal and parietal ROI. The three indicators Seg 1-Seg 3 AUC scores calculated from MSE curves of each signal segment.

Figure 4-6 presents structural equation modelling assessing the effect of APOE ε4. We applied model in panel A on closed and open eyes condition frontal region MSE AUC at low, medium and high scale. Similarly, panel B was applied on parietal region MSE AUC. Table 4-1 gives result of the model estimation.

Table 4-1. Structural models estimation for effects of APOE ε4 on MSE AUC at different ROI, brain state and temporal scales

Condition	Scale Range	Factor Loadings				APOE ε4 effect size
		Frontal Region of Interest				
		F3	F4	FCz	Fz	
eyes closed	low	.92*	.93*	.87*	.91*	-.56*
	medium	.83*	.90*	.95*	.88*	.00
	high	.83*	.97*	.56*	.70*	.09
eyes open	low	.87*	.85*	.67*	.80*	-.50*
	medium	.88*	.92*	.86*	.81*	.36*
	high	.72*	.68*	.90*	.74*	.46*
		Parietal Region of Interest				
		P3	P4	Pz		
eyes closed	low	.90*	.91*	.94*		-.19
	medium	.88*	.91*	.92*		-.17

	high	.88*	.91*	.92*	-.17
eyes open	low	.89*	.90*	.92*	-.48*
	medium	.85*	.73*	.90*	-.04
	high	.80*	.79*	.80*	-.00

All the models were well fitted to the corresponding data according to the standards of model fitting goodness. In the table, the "Factor loading" columns demonstrated the factor loadings of the sub-factors indicating the high-order MSE AUC latent factors. Significantly substantial factor loadings (e.g., above .50) means that the general high-order latent factor could well explain the electrode-specific sub-factors. The "APOE ε4 effect size" column gives the APOE ε4 effect on the higher-order latent MSE variable. For example, -.56 in the first row indicated that under eyes closed condition, APOE ε4 carriers have larger MSE at low scale by 56% of a standard deviation as compared with non-carriers. Table 1 showed that under open eyes condition, MSE of APOE ε4 carriers was larger at low scales and smaller at medium and large scales. Under closed eyes condition, the effect was consistent to open-eyes condition at low scale but diminished at medium and high scale. The above APOE ε4 effect pattern, however, was not prominent for parietal electrode sites, except at low scale under eyes-open condition.

APOE ε4 effect on MSE EO-EC difference

A previous study carried out with a dataset largely overlapping with this current study (Kaur et al., 2019, under review) already found out that MSE measured under closed eyes condition was larger than that under eyes open condition at small scale (1-5), and smaller at higher scale (6-10). The current study has observed similar difference pattern, as shown in Figure 4-7. From the view of dynamics, such difference could be functional. Intuitively, the complexity of brain signal may decrease from closed to open eyes condition because when external stimulus comes, the brain might be more focused (more regular/less complex) comparing to the wandering state during closed eyes condition. Therefore, the difference in signal complexity detected when resting state change from closed to open eyes may characterize the sensitivity of the dynamic neural system to stimuli. The larger difference (more pronounced decrease in complexity from closed to open eyes resting state) may indicate a higher functioning neural system. Therefore, it would be interesting to investigate whether the MSE difference between

open and closed eyes resting state is also associated with APOE ε4. In order to test this hypothesis, a latent difference score model was applied to the current dataset.

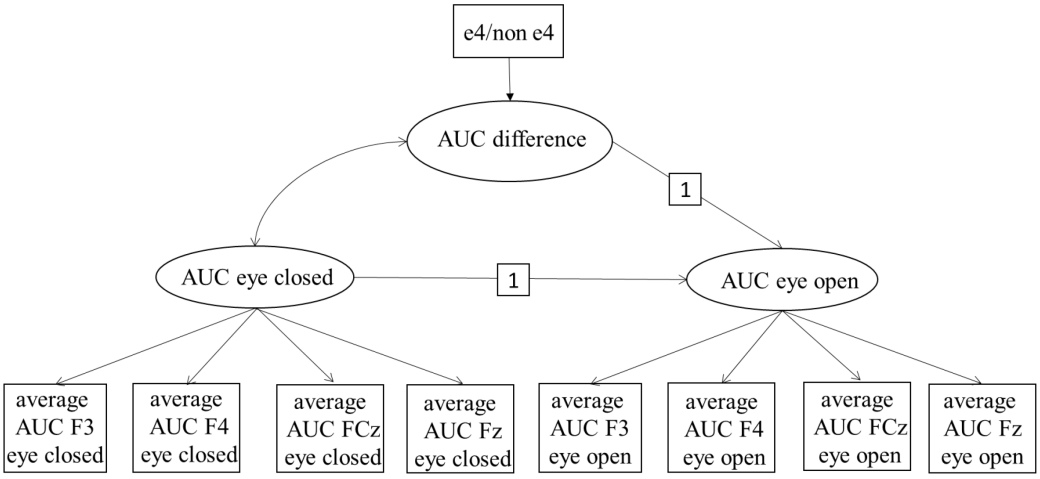

Figure 4-7. Latent difference model exploring APOE ε4 association with difference between eyes open and eyes closed MSE AUC. The observed indicators are means of the AUC scores across the three AUC scores calculated from three EEG segment MSE curves of the electrodes.

Figure 4-7 gives a schematic representation of the difference score model. Since APOE ε4 effect was only prominent at the frontal region, we applied this latent difference model only on the frontal MSE AUC at low, medium and high scales. Regression coefficient of latent variable AUC eyes open on AUC difference and AUC eyes closed were both fixed to 1, indicating that AUC eyes open is completely explained by AUC eyes closed and AUC difference (as illustrated in Figure 4-2). The standardized latent variable of MSE AUC difference was regressed on the ε4/non- ε4 binary variable. The model results are summarized in Table 2.

Table 4-2. Structural equation models estimation for regression effects of APOE ε4 on the latent difference score of EO and EC MSE AUC across temporal scales at central-frontal ROI

Scale Range	EO-EC difference	APOE ε4 effect size
Low	-.12*	.31
Medium	-.40*	.55*

High	.56*	.47*

In Table 4-2, the EO-EC difference column displays the latent score of eyes open MSE subtracting eyes closed MSE. The APOE ε4 effect size column indicates how much variance of the EO-EC difference across individuals can be explained by the ε4/non-ε4 variable. As is already shown in Figure 4-5, EO-EC difference in Table 4-2 can be negative in small and medium scale, but positive in large scale. It means that opening eyes reduce MSE in small and medium scale and increases MSE in large scale. The APOE ε4 effect size in Table 4-2 are visualized in Figure 4-8, where EO-EC on y-axis is the difference of the latent mean scores of eyes open and eyes closed MSE.

According to Figure 4-8, the MSE EO-EC difference is significantly differed between APOE ε4 carriers and non-carrier at medium and high scale ($p < .05$). At medium scale, the absolute difference between eyes open and eyes closed MSE of APOE non ε4 carriers is significantly smaller than carriers, whilst at high scale, the absolute difference is larger among non-ε4 carriers than carriers. As compared with results of low and high scales, we focus on result of medium scale, because medium scale MSE reflect more properties of the nonlinear dynamics and dominate oscillation frequency bands (such as alpha oscillation) of the resting state EEG. The low scale result reflects most linear dynamics of the EEG and signal noise, which is not meaningful for the indication of brain signal complexity. High scale result is not robust enough as compared with medium scale because of the MSE reliability issue. Therefore, we apply our interpretation of the MSE difference only on the medium scale.

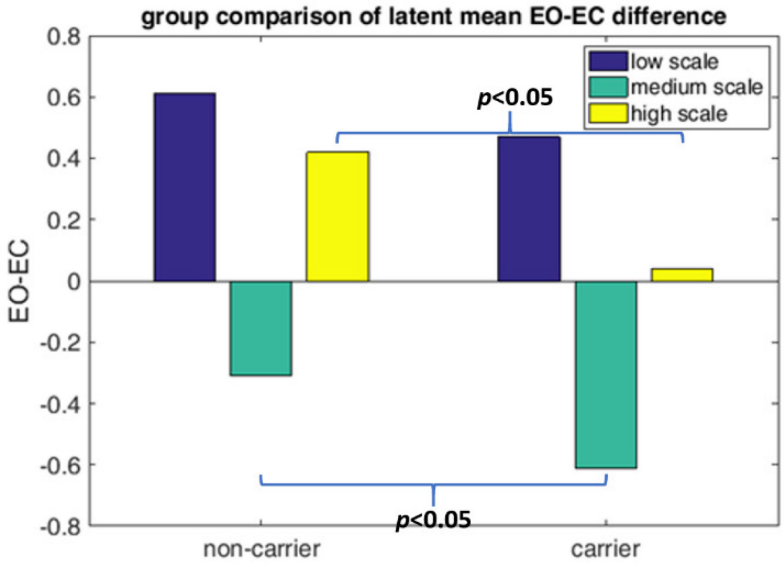

Figure 4-8. Comparison of eyes open-eyes closed MSE difference at different scales with respect to ε4 carrier/non-carrier.

The key finding of the current study is as follows: APOE ε4 allele was associated with larger MSE at scale 1-4 but smaller MSE at larger scales, and this association was more consistent at central-frontal electrodes than at parietal region. At low scales the association was indistinguishable for EO and EC conditions but at higher scale, it was most pronounced during the EO condition. As compared with non-carriers, EO – EC difference of ε4 carriers is similar at low scale, but becomes larger at medium scale, indicating more sensitive brain system to stimulus input.

4.2 Effect of APOE polymorphism on the Multiscale Entropy of closed and open eyes resting state in healthy young individual adults

In the last section, the association between APOE genotype and brain signal complexity was discussed. As part of genotype-phenotype relationship investigation, APOE ε4 should also be studied in terms of its association with cognitive behavior, so that the gene – brain and gene – behavior studies could be connected via gene, and therefore construct the framework of gene – brain – behavior relationship study. In this session, I will focus on the investigation of APOE polymorphism and cognitive performance (Working Memory Capacity and Reasoning); the text will be adapted from my accepted paper. The general aim of this study was to explore the effects of APOE polymorphisms on working memory capacity (WMC), secondary memory (SM) and reasoning (fluid intelligence, gf) in young adulthood. Previous research suggests that the APOE polymorphisms might differ in their influence on the

domains of WMC, SM and gf. However, due to the strong associations between these cognitive phenotypes, genotype differences should follow similar patterns across cognitive domains. We argue that the study of genotype differences should be carried out at the level of latent variables in order to generalize beyond task specificity and measurement errors. The main expectation was that the latent variable approach would shed light on the generalizability of the effects across task classes and would contribute to establishing robust results.

As is introduced in Chapter 1, it is well established that elderly carriers of at least one APOE ε4 allele – even if not diagnosed with dementia – may exhibit impaired global cognitive performance (Small et al., 2004; Wisdom et al., 2011). However, whether APOE ε4 exerts positive or negative effect on cognitive performance among young healthy adults remains unclear and there are a number of studies with inconsistent conclusions (Rusted et al., 2015). The relatively better performance of young APOE ε4 carriers as compared with non-ε4 carriers has been explained by antagonistic pleiotropy, where an allele increases the chances for reproduction early in life and only later on has a negative influence on fitness or survival (e.g., Han & Bondi, 2008).

Latent variable construct of WMC

So far, studies on APOE and cognitive abilities exclusively relied on observed test scores, which does not allow generalizing above individual differences captured by single tests (e.g., Wacker et al., 2012, for personality and the Catechol-O-methyl-transferase gene). In contrast, multivariate assessments used to estimate latent variables allow to account for measurement error and method specificity and thus capture individual differences at the level of abilities beyond single task performance.

Working memory capacity (WMC) is a central cognitive construct, indicating a persons' capacity to bind and flexibly update information in short-term memory (e.g., Wilhelm et al., 2013). There are plenty of measures that have been used to capture this ability. Importantly, it has been recognized that indicators from multiple tasks are necessary to control for irrelevant variance components and to generalize measurements to the construct level (Schmiedek et al., 2014). Wilhelm et al. (2013) showed that the capacity of building, maintaining and rapidly updating arbitrary bindings accounts for a large amount of common variance across all traditionally applied WMC tasks, such as updating, n-back, and complex span. Thus, a latent

variable indicated by assessments belonging to any of these task classes is expected to be good measure of individual differences in WMC as cognitive phenotype. However, because every single task is capturing additional method specific variance, performance on single tasks needs to be considered in the context of other tasks (see for example Schmiedek et al., 2009; 2014).

Another theoretical approach to WMC distinguishes between it's primary and secondary components (e.g., Unsworth et al., 2014). Primary memory (PM) refers to the memory capacity used for short-term information storage and direct processing of information, whereas secondary memory (SM) is the capacity to store, keep and recall information in a long term. Aiming to establish the role of SM in WMC, correlational studies have explored the mediation effect of SM on the relationship between WMC and fluid intelligence (gf; Unsworth and Spillers, 2010; Unsworth et al., 2014; Shipstead et al., 2014). Hence, the above-mentioned research on SM, indicates that SM is an important cognitive ability to be considered along with the working memory system. Additionally, further studies argued that WMC and reasoning are nearly isomorphic abilities (Kyllonen and Christal, 1990; Süß et al., 2002). The binding theory of WMC mentioned above (Oberauer et al., 2007) explains this strong association by the involvement of mental representations of novel structures that are necessary for solving both, WMC as well as gf tasks.

To summarize, working memory capacity is well established as a crucial domain of cognitive functioning (e.g., Baddeley and Hitch, 1974; Wilhelm et al., 2013). There is robust evidence supporting the strong correlations of WMC with SM and gf (Engle et al., 1999; Kyllonen and Christal, 1990; Oberauer et al., 2005) and its generalizations across different measurement paradigms (Süß et al., 2002). APOE effects on these cognitive domains among young, healthy adults have already been studied but only on the level of single tasks, yielding inconsistent results. Thus, we argue that the study of APOE effects on cognitive abilities should include multiple measures and latent variables representing WMC, SM and gf.

Samples and Measurements

The study sample used for the current study is described in the sample session of Chapter 2 (Table 2-1). In the following text of this current study, Sample 1 in Table 2-1 will be referred to as Sample 1, combination of Sample 2 and 3 in Table 2-1 with exactly same APOE and cognition task measurements will be referred to as Sample 2, Sample 4 in Table 2-1 will be

referred to as Sample 3 and Sample 5 in Table 2-1 will be referred to as Sample 4. Table 2-1 also showed that there are crucial assessments overlapped between samples. Next, we provide short descriptions of the all the tasks used in the present study. These tasks were also applied and evaluated by Wilhelm et al. (2013). Task-specific indicators used in each sample are summarized in Table 2-1. Further details on the task procedures can be found in Wilhelm et al. (2013).

Binding tasks (Binding) The binding task included 15 trials for the letter-color domain (Bind_lc) and 14 trials each for the word-number domain (Bind_wn) and the location-letter domain (Bind_ll). In each trial, participants were presented with a sequence of item pairs specific to the task domain and asked to memorize the association. For example, in the letter-color binding task, sequences of letter-color pairs were provided. The trial length was 1 s with 3 s-intervals for the letter-color task, 2 s with 1 s-intervals for the word-number binding task, and 1.5 s with 500 ms-intervals for the location-letter binding task. Participants were asked to recall the associations immediately after presentation. Illustration of verbal-numerical biding was represented in Figure 4-9, panel B. For all binding tasks, the number of pairs within trials ranged between two and six (load level).

Updating tasks (Updating) Each updating task included 12 trials; in each trial, a series of two to five randomly selected items (words, digits or positions within a 3*3 grid) were presented on the screen. The presentation durations for the verbal and spatial-figural updating tasks depended on the load level of a given trial (level 2: 2 s; level 3: 2.4 s; level 4: 2.8 s; level 5: 3 s), while for the numerical updating task the presentation duration was 1.6 s for each trial; inter-stimulus intervals were 500 ms. Participants were to update and memorize the last item for each semantic category and to report the last item that had appeared in the trial. Illustration of the verbal updating task was represented in Figure 4-9, panel D.

Recall 1-back (RNb) In the verbal RNb task (RNb_v), participants were presented with one to three boxes per trial (depending on load level). Each box contained a letter and as soon as a new letter appeared in a box, participants were to type in the letter, which just before had been associated with that box. In the numerical RNb task (RNb_n) the procedure was the same except that digits were presented instead of letters. In the spatial-figural RNb task (RNb_f), participants were shown one to three figures (depending on load level) randomly placed within a 3*3 grid. When a figure was presented in a new position in the grid, participants responded by mouse click to indicate the position in the grid where the figure has been shown

just before. In the verbal task, the presentation of each stimulus lasted for 2.5, 3.0, and 3.5 s for load level 1 to 3, respectively. In the numerical task the presentation durations for single stimuli were 2.5, 2.9, and 3.1 s, for load levels 1-3, respectively. Illustration of verbal RNb task was represented in Figure 4-9, panle A. For the spatial-figural task, the corresponding presentation times were 2.5, 3.5, and 4.5 s.

Complex span tasks (CSpan) During the reading (CSpan_v; Kane et al., 2004), operation (CSpan_n), and rotation (CSpan_f) span task, participants were to remember the order of letter presentation (for reading span), order of word presentation (for operation span) or recalling a sequence of arrows with different length and pointing directions (for rotation span), while processing a secondary task in parallel. The secondary task was to identify the semantic correctness of a sentence (for reading span), the correctness of an equation (for operation span) or the correctness of direction of letters. Illustration of rotation span task process was presented in Figure 4-9, panel C. All items for the secondary tasks were presented on the screen. Each complex span task included 12 trials.

Memory updating (MU) This task, only used in sample 3 (see Table 2-1), was adapted from Oberauer et al. (2000). In a 3*3 grid, single-digit numbers were continuously presented. Participants were required to memorize them. Subsequently, arrows with up or down direction appeared in individual cells of the grid. For up-pointing arrows, participants need to mentally add “1” to the digit presented in that cell. For down-pointing arrows, participants need to mentally decrease the number by “1”. After a series of updating steps, participants needed to indicate the final digit for each cell. The experiment included 18 trails.

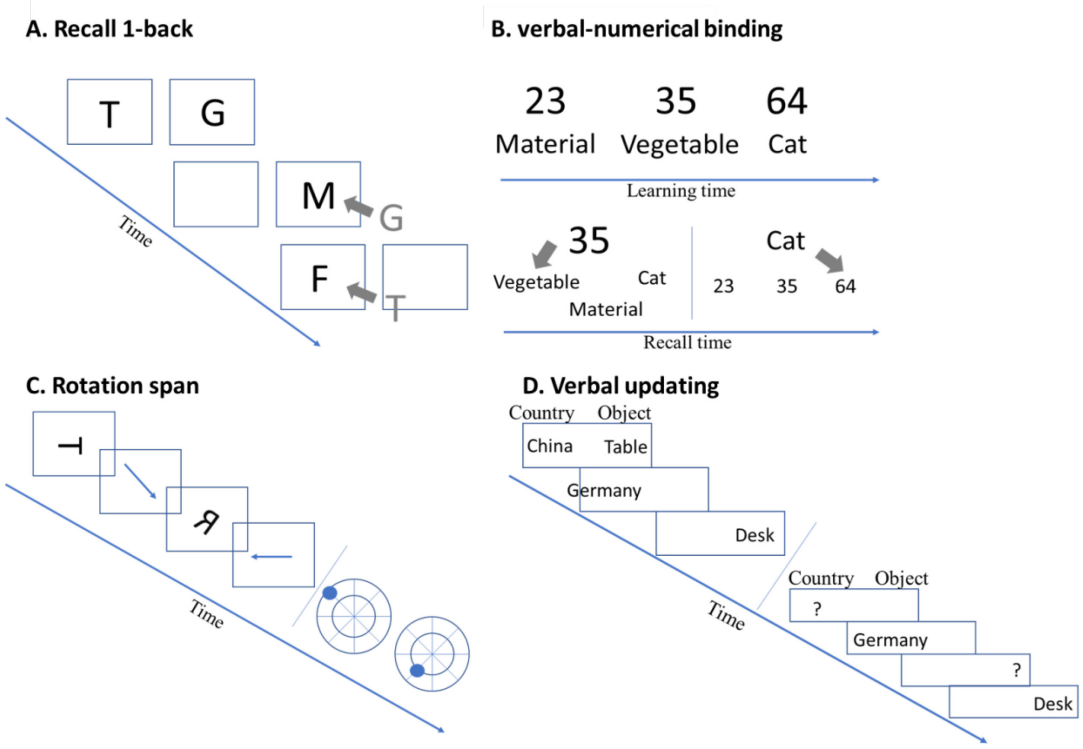

Figure 4-9. Schematic illustration of verbal recall-1-back task (Panel A), verbal-numerical binding task (Panel B), rotation span task (Panel C) and verbal updating task (Panel D).

Secondary memory tasks (SM) The SM tasks were very similar to the binding tasks but did not require immediate recall. In the word-word task (SM_v), two blocks of 20 word pairs each were successively presented, while in the word-number task (SM_n) two blocks each of 20 pairs of a word and a two-digit number were shown. In the letter-position task (SM_f), in a given block, 12 letters were paired with 12 positions in a 4*4 grid. All stimulus pairs were presented for 4 s, separated by intervals of 1 s. After the learning phase participants completed an intervening task, which took about 3 min. Then, participants were to recall the paired information in response to either the first or the second element of the pair.

Fluid intelligence (gf) Fluid intelligence was measured with the Berlin Test of Fluid and Crystallized Intelligence (BEFKI; Wilhelm et al., 2013) in Sample 1. Participants were to solve a series of verbal (gf_v), quantitative (gf_n) and figural (gf_f) deductive reasoning problems. Possible solutions were provided as multiple-choice items. Each task included 16 problems to be completed within 14 min. In Samples 3 and 4 fluid intelligence was measured with 16 items from the Raven's advanced progressive matrices (Rav; Raven et al., 1998).

Data treatment and scoring

For coding education level, we contrast participants without high school degree (coded as 0) and with high school degree (coded as 1). A product term genotype * education was also calculated. As shown in Table 4-3, the education and genotype * education variable can only be reasonably calculated in Sample 1, which includes enough participants without high school degree in both, APOE ε4 carrier and non-ε4 carrier groups, for providing robust estimates.

Table 4-3 Demographic information stratified by ε4 carrier and non- ε4 carrier group

Genotype group	sample 1	sample 2	sample 3	sample 4
Mean and standard deviation of age				
Non-ε4 carrier	27.7(4.9)	23.4(3.7)	26.0(4.4)	27.7(5.7)
ε4 carrier	26.9(4.8)	23.6(3.3)	25.7(4.7)	27.7(4.9)
Frequency of female/male participants				
Non-ε4 carrier	100/82	156/50	90/92	80/70
ε4 carrier	39/25	60/31	34/28	22/29
Frequency of no high school degree / high school degree				
Non-ε4 carrier	46/136	10/195	39/143	39/111
ε4 carrier	23/41	5/86	10/52	10/41

For each performance indicator univariate distributions were visually screened for outliers and distribution shapes. Observations outside the 1.5 inter-quartile range (i.e., outside the whiskers in a boxplot) were defined as univariate outliers (Tukey, 1977). Among the 245 participants in Sample 1 with genetic data, there were 32 missing values out of 4410 data points. Univariate outliers in the psychometric measurements were included in the missing values. Multiple random imputation (Allison, 2001) was applied to replace the 32 missing values. This imputation scheme was used because the proportion of missing values was less than 0.5% (Dong & Peng, 2013). It is theoretically necessary that the variables for imputation meet assumption of normal distribution, which was partly violated by 6 indicator variables in

our sample; however, the normal model used in our imputation procedure performed well even for non-normally distributed variables (Schafer, 1997). Among the 18 task measurement indicators described in the measurement session (see Table 2-1), ten indicators did not have outliers. There were no outliers in the inter-individual distributions in Samples 2, 3 or 4 and only 1 participant with 3 missing data points in Sample 2. These missing points were list-wise deleted in model estimation.

Statistical Analysis

Structural Equation Modeling (SEM) was applied to the data from all four samples. However, due to different numbers of WMC, SM and gf indicators, the models differ across samples. In the first sample, we were able to model four latent factors of WMC, along with a higher-order factor representing general WMC. Additionally, we modeled a latent factor of SM and another latent factor gf that were both correlated with each other and with the general WMC factor. This model had been established previously by Wilhelm et al. (2013) with the same dataset. In the present work, all three latent factors were regressed onto the dummy variables described above, coding genotype groups, as well as education level and the genotype*education product term. Regression weights of the dummy variables thus indicate genetic and education effects and their interaction on the general WMC factor, SM and gf.

Based on the available assessments (see Table 2-1) in Sample 2, we modeled two task-specific WMC factors. Because there were only two WMC factors in this model, no higher order WMC factor was modeled but task specific factors were allowed to correlate. No SM and gf assessments were available in this sample. Task indicators for the WMC factors were measured in trials with different load levels. Therefore, we also tested the genotype group differences for variables with different difficulty levels.

In Sample 3 there were two indictors for WMC and one for gf (see Table 2-1). We used these indicators for modeling a WMC/gf latent variable, regressed onto the genotype-coding variables. Finally, Sample 4 contributed with a latent gf factor estimated by performance in the Raven test.

As mentioned above and illustrated in Table 2-1, some of the assessments overlapped across studies. As a final analysis step we merged samples 1 and 2 and investigated the genotype and education effects by means of a categorical regression analysis including verbal and spatial-

figural RNb tasks available in both studies. Similarly, samples 1 and 3 were merged to analyze genotype-education-phenotype relations based on the rotation span task (CSpan_f).

Results provided by Sample 1

The WMC, SM and gf factors estimated in the model established by Wilhelm et al. (2013) were first regressed onto the dummy variable, contrasting APOE ε4 carriers with all other genotype groups (Model 1). In a second step (Model 2), the factors in the same psychometric model were regressed onto two coding variables contrasting APOE ε4 carriers with non-ε4 carriers, as well as different education levels (without and with high-school degree) along with the product term of genotype and education. Additional results illustrating single factors of WMC, SM and gf regressed onto the same genotype-coding variables are provided in Table 4-4.

Table 4-4. Structural models estimation for effects of APOE ε4, education and their interaction on working memory capacity single factors

Factors	$\chi^2(df)$	CFI	RMSEA	SRMR	genotype	education	interaction
Binding	7.98(6)	.98	.03	.02	-.73*	.21	.76*
Updating	2.39(6)	.98	.00	.01	-.46	.19	.23
RNb	7.11(6)	.99	.02	.02	-.75*	-.04	.78*
CSpan	3.58(6)	1.00	.00	.01	-.16	.56*	-.18
SM	6.07(6)	1.00	.00	.02	-.39	.37*	.42
gf	9.65(6)	.97	.05	.02	-.71*	.12	.72

Note. * *p*-value < .05; Binding – binding tasks; Updating – updating tasks; RNb: recall 1-back; CSpan – complex span tasks; SM – secondary memory tasks; *df*-degree of freedom; CFI – Comparative Fit Index; RMSEA – Root Mean Square Error of Approximation.

Because the model depicted in Figure 4-10 has been established by Wilhelm et al. (2013) with the same sample data, we built upon this previous work and did not test alternative model structures for describing the cognitive phenotypes. The common variance among the four

WMC task clusters (Binding, Updating, RNb and CSpan) was captured by a higher order WMC factor. Loadings on the task-specific factors were substantial. A further latent variable accounted for common residual variance among verbal-numerical content (VN). In addition to WMC, the model included SM and gf as correlated factors. Method-specific variance induced by multiple applications of paired associate tasks (Passo) was captured by a method factor.

In Model 1, the standardized latent variables WMC, SM and gf were regressed onto the dummy variable contrasting APOE ε4 carriers with all other genotype groups. The model fitted the data very well: χ^2 (133) = 192.25, CFI = .97, RMSEA = .04, SRMR = .04. All factor loadings indicated in Figure 4-10 were significant. The figure further shows that WMC, SM and gf were highly but not perfectly correlated. Thus, APOE effects are expected to be similar in magnitude for all cognitive ability factors. The regression weights testing gene effects (see Fig. 4-10), can

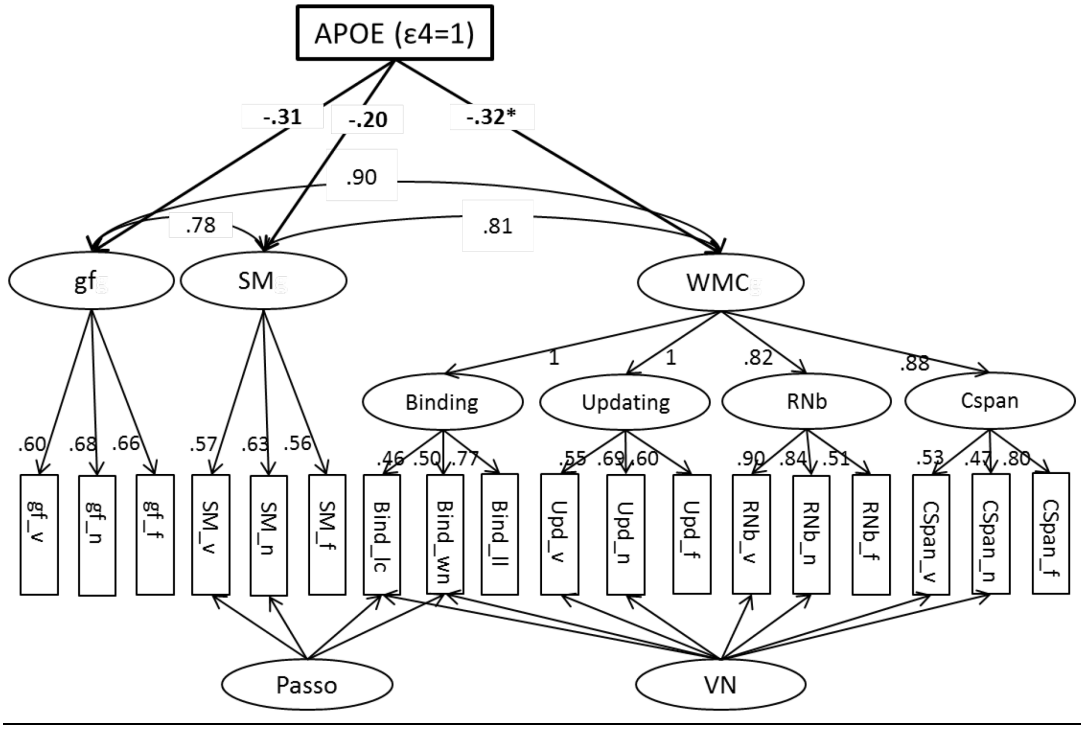

Figure 4-10. Schematic representation of structural equation model exploring APOE ε4 effects on working memory capacity (WMC), secondary memory (SM) and fluid intelligence (gf).

be interpreted as differences between genotypes in terms of standard deviations, because the latent variables were standardized and the predictor (genotype) was dummy-coded. The genetic effects (see Fig. 4-10) were negative, indicating that WMC in APOE ε4 carriers is worse – by about 1/3 of a standard deviation – as compared with non- ε4 carriers. The APOE

ε4 effect on WMC was statistically significant (WMC: -.32, p = .04). APOE ε4 effects on SM and gf were somewhat smaller but also negative and the effect did not reach conventional significance levels (SM: -.2, p = .26; gf: -.31, p = .07), possibly due to the limited sample size. In summary, the data collected in Sample 1 revealed worse cognitive performance in young carriers of APOE ε4 as compared to non-carriers.

In Model 2, the standardized latent variables WMC, SM and gf, configured in the same way as in Model 1, were regressed onto the dummy coded gene and education variables, as well as their product, testing the interaction between education and genotype group. The model fitted data very well: χ^2 (163) = 230.7, CFI = .97, RMSEA = .04, SRMR = .04 and all factor loadings were statistically substantial. The interaction effects were as follows: WMC – .32, p = .33; SM – .06, p = .86; gf – .83, p = .02. Thus, the genotype * education interaction was statistically substantial for gf only, but all cognitive measures pointed into the same direction, suggesting lower cognitive performance of APOE ε4-carriers specifically in participants with lower education level. Representation of Model 2 was displayed in Figure 4-11.

In order to visualize the interaction at the level of latent factor means, we conducted a multiple group structural equation modeling on Sample 1, which allowed estimating latent means of WM, SM and gf for different groups. Participants were separated into four groups: APOE ε4 carriers with high school degree (N11 = 41), ε4 carriers without high school degree (N12 = 23), non-ε4 carriers with high school degree (N13 = 136) and non-ε4 carriers without high school degree (N14 = 46). In this model the latent variables were scaled by a reference indicator, latent means and variances were freely estimated across groups and model parameters were fixed to be equal across groups. The latent means of WMC, SM and gf for the four groups are illustrated in Figure 4-12. The figure shows no performance difference between genotypes in the group with higher education. However, performance of APOE ε4 carriers in WM and gf was worse in the group with low education. Due to the fact that within-group sample sizes were rather small these estimates of latent mean differences may not be very robust, but they indicate a plausible finding on gene-environment interaction.

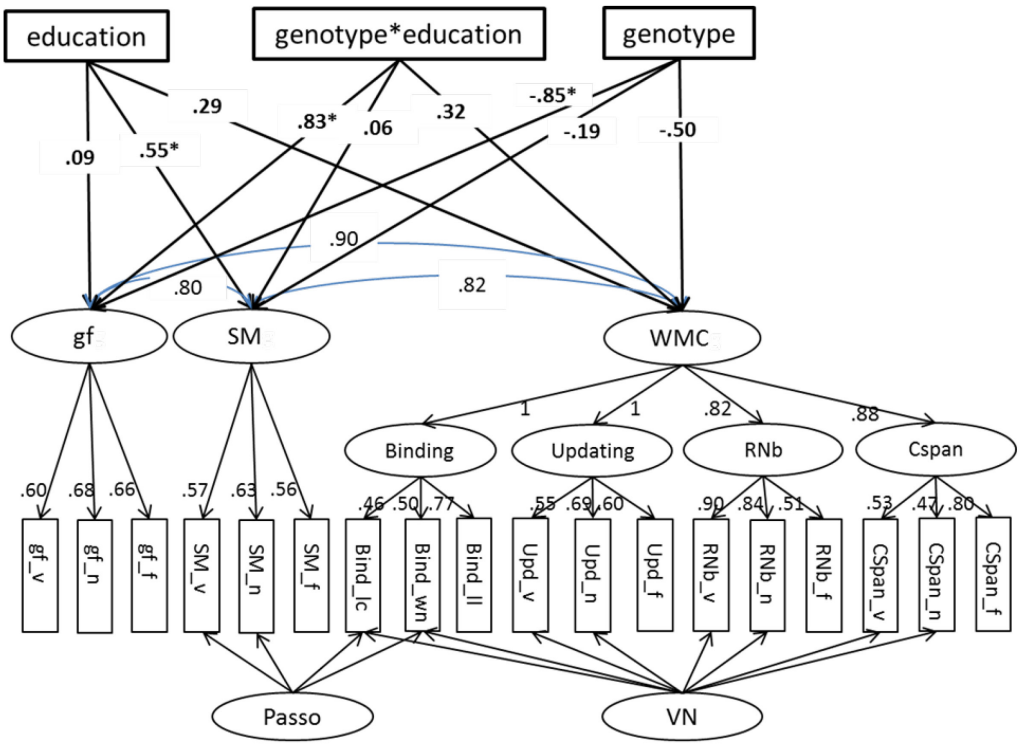

Figure 4-11 Schematic representation of structural equation model exploring APOE ε4, education and the gene*education interaction effect on working memory capacity (WMC), secondary memory (SM) and fluid intelligence (gf).

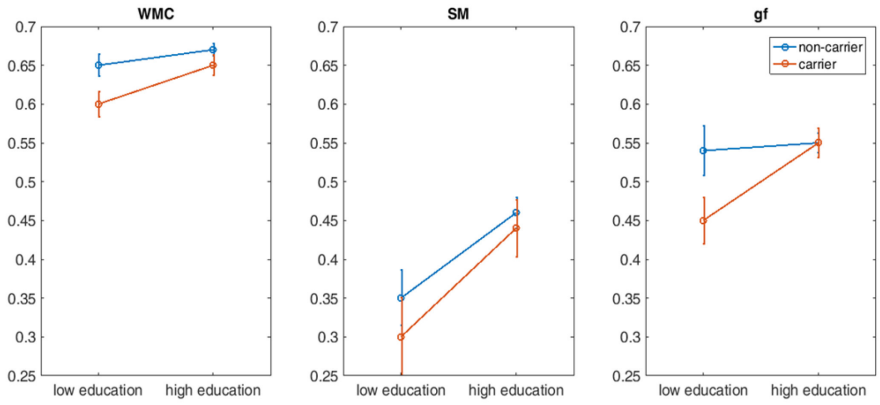

Figure 4-12. Interaction plot visualizing differences in latent means of WMC, SM and gf for genotype groups split by education. Blue lines indicate latent means differences for non-ε4 carriers. Red lines indicate differences for ε4 carriers.

Summarizing the results of Sample 1, young carriers of at least one APOE ε4 allele showed worse cognitive abilities as compared with non- ε4 carriers. This negative APOE ε4 effect, however, only holds for ε4 carriers with lower education.

Results provided by sample 2

In Sample 2 there were fewer WMC assessments than in Sample 1, yielding only verbal and figural WMC task data but from the same RNb tasks as applied in Sample 1. Average performance across three blocks of trials per task with different levels of difficulty (load levels 1, 2 and 3) were used as indicators for modeling a verbal and a figural WMC factor (see Fig. 4-12). In Model 3 the two factors were allowed to correlate and were both regressed onto the dummy variable contrasting APOE ε4 carriers with non-ε4 carriers. Model 3 fitted the data very well: χ^2 (12) = 24.4, CFI = .97, RMSEA = .06, SRMR = .04; all factor loadings were significant and of considerable magnitude. However, the loading structure was slightly heterogeneous because the item block of high difficulty (load level 3) discriminated least between individuals with high and low WMC. For the verbal WMC task domain, the medium difficulty task had best discriminative power. Overall, and contrary to Sample 1, young APOE ε4 carriers showed better performance, especially in the figural domain. The opposite effects in Sample 1 and Sample 2 were similar in magnitude. Sample 2 showed statistically significant differences of about 1/3 SD between APOE ε4 carriers as compared with the non-ε4 genotype groups (regression weights and significance level: RNb_v: .26, p = .03; RNb_f: .33, p = .03). However, as described above, APOE ε4 carriers in Sample 2 were rather highly educated. Because of the very scarce number of APOE ε4 carriers with low education in Sample 2, education could not be tested as moderator.

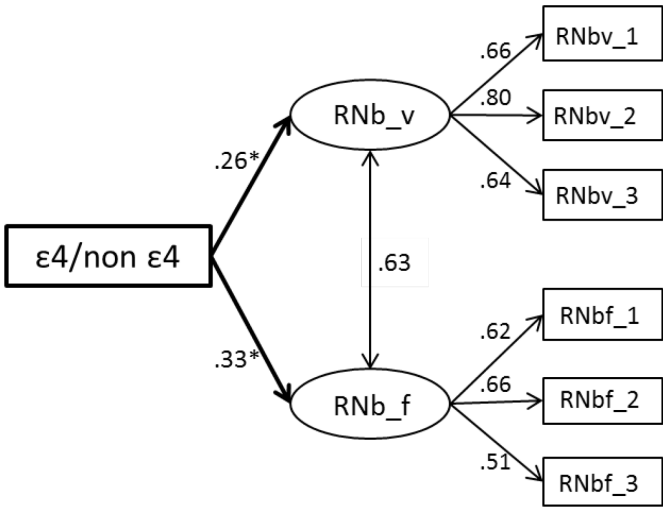

Figure 4-13. Schematic representation of structural equation model (Model 3) exploring APOE ε4 effects on working memory capacity (WMC) indicated by verbal (RNb_v) and figural (RNb_f) recall-1-back task as compared with non-ε4 carriers.

Above education level, APOE ε4 effects may be moderated by task difficulty, assuming that more difficult tasks require the neurocognitive system to dynamically respond to varying challenges (Craik and Byrd, 1982). Since factor loadings of the indicators with different difficulty levels were heterogeneous in Model 3 (Fig. 4-13), we tested genotype effects as a function of task difficulty. Table 4-5 provides standardized regression weights and significance levels. For all load levels, the regression weights corresponded to performance advantages in favor of APOE ε4 carriers of < .25 SDs. Thus, for both verbal and figural tasks, categorical regression analyses revealed numerically, but not significantly better WMC performance by APOE ε4 carriers. Taken together, Sample 2 suggested that the ε4 allele positively influenced cognitive performance but the effects were small and could not be statistically established.

Table 4-5. Regression weights illustrating APOE ε4 effect on RNb for different load level

	Load level 1	Load level 2	Load level 3
RNb_v	.10 (p = .07)	.08 (p = .13)	.07 (p = .2)
RNb_f	.09 (p = .09)	.06 (p = .28)	.13 (p = .02)

Results provided by sample 3

In Sample 3, we estimated a latent variable gf/WMC by means of three cognitive tasks: the rotation span task (CSpan_f), also used for Sample 1, the memory updating task (MU) and Raven's progressive matrices (Rav). We then regressed gf/WMC onto the dummy-coded variables, following a similar coding scheme as for Sample 2 (Fig. 4-13). The model fit was good: χ^2 (2) = 5.72, CFI = .98, RMSEA = .09, SRMR = .03. Model 4 tested the effect of ε4 on gf/WMC as compared with non-ε4 carriers: gf/WMC: .19, p = .26. Results did not reveal a significant effect of APOE ε4 allele on gf/WMC, even though numerically the effect was positive.

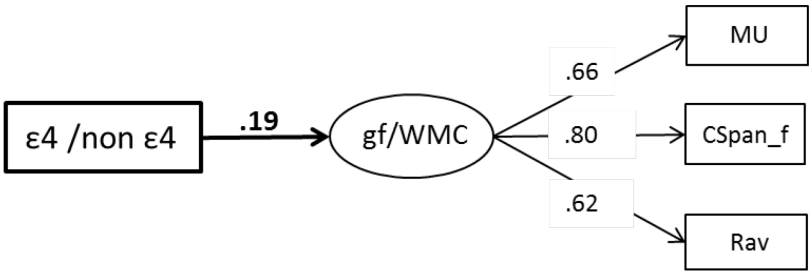

Figure 4-14. Schematic representation of structural equation model (Model 4) exploring the difference between ε4 carriers and non-carriers in the latent factor gf (fluid intelligence).

Results provided by Sample 4

In Sample 4, a latent gf variable was estimated by three indicators provided by the Raven test (Rav 1-3, three item parcels). Similar to Sample 3, the latent variable of gf was regressed onto the dummy-coded genotype variable following the same coding scheme. The model fit was very good: χ^2 (2)=0.52, CFI=1.00, RMSEA=.00, SRMR=.02. Model 5 is depicted in Figure 4-14 and indicates a positive – albeit non-significant – effect of the APOE ε4 allele on gf: .23, p = .28).

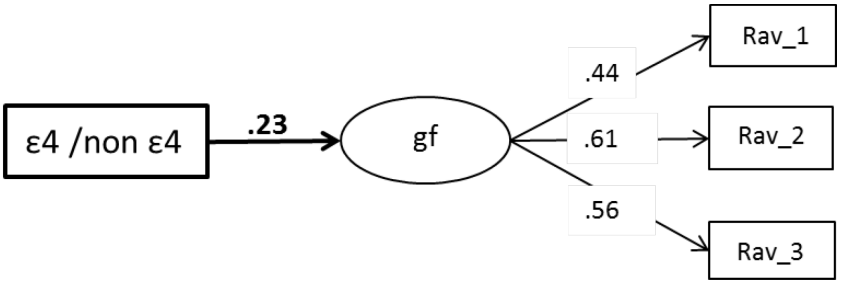

Figure 4-15. Schematic representation of structural equation model (Model 6) exploring differences between ε4 carriers and non-carriers in the latent factor of gf.

Results based on1 merged samples 1 and 2

Data from samples 1 and 2 overlapped in two performance indicators: Verbal recall 1-back (RNb_v) and Figural recall 1-back (RNb_f). For a more powerful test, we obtained general RNb_v and RNb_f measures for Sample 2 by averaging difficulty level-specific task indicators and merged the data of samples 1 and 2, allowing to test genotype effects in a much larger sample of 556 participants in total. In the merged sample, there were 56 non-ε4 carriers without and 331 with high school degrees, 28 ε4 carriers without and 127 with high school degrees. Performance for the two overlapping indicators were regressed onto the genotype

variable contrasting APOE ε4 carriers against non-ε4 carriers in separate samples split by education level. The results of four linear regression models with categorical predictors (summarized in Table 4-6) revealed that in the sample with high school degree, both figural and verbal RNb performance was better among ε4 carriers as compared with non-carriers. The positive ε4 effect was significant for figural RNb. In the sample without high school degree, both figural and verbal RNb performance tended to be worse for ε4 carriers as compared with non-carriers, but the effect was not statistically significant.

Table 4-6. Regression weights illustrating APOE ε4 effect on RNb in merged sample

	ε4 effect in the lower-education sample	ε4 effect in the higher-education sample
RNb_f	-.20 (p = .06)	.09(p = .04)
RNb_v	-.12 (p = .12)	.06(p = .17)

Results based on merged samples 1 and 3

Similar to merging samples 1 and 2, we also combined sample 1 and 3 with respect to rotation span performance (CSpan_f). Based on the merged samples, we conducted a linear regression analysis testing the overall ε4 allele effects as compared with non-ε4 carriers on CSpan_f performance in a larger sample with 489 participants in total, providing more statistical power. The results revealed no genotype effects, neither in the split sample with higher education nor with lower education. Regression weight for the split sample without high school degree was .02, p = .53, and for the split sample with high school degree it was -.00, p = .9.

To summarize, we can conclude from the current study that the APOE ε4 effect on cognitive ability of young adults is generally complex. The ε4 allele tends to be negatively associated with cognitive performance in individuals with lower education levels, there might be a slightly positive association in persons with higher education – a finding which that is partly in line with the antagonistic pleiotropy view on APOE and cognitive ability.

4.3 Combined discussion

To summarize, in this Chapter, individual difference in the relationship between gene and brain, as well as gene and behavior were largely discussed based on young healthy population. The principal aim was to enrich existing knowledge on the early diagnosis of Alzheimer Disease by comparing the phenotype of those people with and without genetic risk for AD. However, because of limited sample size, there's only around 70 participants with both EEG and WMC recordings, which is a very small sample size and impossible for the application of structural equation model connecting the gene, brain and behavior measurements togethers. Therefore, here I will discuss the results from the two studies first separately, then jointly for deeper understanding of the gene-brain-behavior relationship basing on the available datasets.

Discussion based on 4.1

The study in 4.1 assessed the APOE ε4 association with brain signal complexity. Multi-scale entropy (MSE) was used in my study to index brain signal complexity. This study found out that 1) APOE ε4 allele was associated with more complex brain signals at scale 1-4 but more predictable (regular) and less complex signals at larger scales. 2) This association was more consistent at central-frontal electrodes than at parietal region. 3) At low scales the association was indistinguishable for EO and EC conditions but at higher scale, where the association reversed, it was most pronounced during the EO condition. 4) As compared with non-carriers, EO – EC difference of ε4 carriers is similar at low scale, but becomes larger at medium and high scale, indicating more sensitive brain system to stimulus input. Below I will discuss the findings in more details.

Genetic association with MSE at lower vs higher temporal scales

At low temporal scale, increased MSE was detected among APOE ε4 carriers under both eyes open and eyes closed conditions across the cortex. At medium and high temporal scales, ε4 carriers showed lower MSE than non-carriers. As interpreted by Costa et al. (2005) who proposed the original MSE algorithm, MSE evaluates the complexity of time-series signal basing on the temporal scale. At lower scale (e.g. scale 1-4), MSE estimation mainly characterizes how unpredictable the time series is. At higher scales (e.g., scale factor >4), MSE may reflect the long-range temporal correlation, which is defined as the "complexity" of the time series on a multiple-time-scale basis. According to this interpretation, the complexity of MSE is more likely to be characterized by increased MSE estimation at higher scale.

Therefore, the finding of the current study that ε4 is associated with decreased MSE estimation at higher scale may index less signal complexity of ε4 carriers. Meanwhile, consistently increased MSE detected at lower scales which characterized higher irregularity of the brain signal may be possible to be developed as a valid biomarker. Since a previous study (Yang et al., 2013) failed to conclude any BOLD complexity difference across APOE genotypes among the young adults, our study could add information to current knowledge gap.

Genetic association with MSE under EO & EC measurement condition

In previous studies on APOE association with resting state EEG complexity, EEG recordings were usually acquired under single measurement condition (e.g. EC condition, Mizuno et al. 2010). However, since the brain is under different dynamic states and activation patterns (Marx et al., 2004) under EC and EO conditions and their MSE curves show different pattern (Hussain et al., 2017), it is necessary to include resting state conditional difference when investigating MSE association with gene.

In this study, from observation of the pattern of MSE curves when comparing EO and EC conditions at frontal electrode sites, we found crossing points between low and medium scale, as well as medium and high scale. Thus we grouped those higher time scales 4-20 into medium scale (5-10) and high scale (11-20) and revealed that the effect sizes of APOE ε4 on high-scale MSE were larger than that on medium scale under EO condition (as is displayed in Table 4-1). But for ε4 carriers, the magnitude of EO – EC difference is larger at medium scale and smaller at high scale (Table 4-2). If we focus on medium-scale EO-EC difference and interpret the difference as sensitivity of dynamical neural system when interrupted with external stimulation from closed to open eyes (Kaur et al., 2019), then APOE ε4 might be associated with this sensitivity, which indicates a facet of brain activation process.

Discussion based on 4.2

The general aim of study 4.2 was to explore APOE genotype effects on cognitive abilities in young adulthood. Results can be summarized as follows: 1) Generally, APOE ε4 effects on cognitive performance were not unequivocal. 2) Cognitive performance in different genotype groups depended on education level. In low-education groups, APOE ε4 carriers performed worse than non-ε4 carriers. However, in participants with higher education (i.e., above high-

school degree) cognitive performance was statistically indistinguishable between APOE ε4 carriers and non-carriers, even though genotype effects tended to be numerically slightly positive in favor of APOE ε4-carriers.

Genetic association with cognition

Sample 1 revealed statistically significant negative APOE ε4 effects on WMC, assessed as a latent variable integrating performance in updating, binding, recall N-back and complex span tasks. However, in Sample 2, the effect reversed, even when the genotype effect was tested separately on WMC tasks with different levels of difficulty. Moreover, although not statistically significant, the reasoning factor established in Samples 3 and 4 was associated with APOE ε4 in the same direction as in Sample 2, that is, ε4 carriers performed better than non-carriers. Thus, overall, we are inclined to conclude that at least in some cases the effect of the APOE ε4 allele is negative; in other cases it is not conclusive. The conclusions in the literature are possibly mixed because of varying roles of education. Furthermore, results provided by Sample 1 revealed that the ε4 effect on WMC, SM and gf differed, even though the three latent variables themselves were highly correlated (see Figure. 4-10). As revealed by Model 2, the ε4 effect on gf was much larger than on SM and WMC, indicating that gf might be more strongly influenced by the genotype than the other functions. In Sample 3, the combined gf/WMC factor was estimated on the basis of a broader variety of task types including both reasoning and WMC assessments than in the other samples, and thus, these two highly correlated but not completely isomorphic latent variables were confounded. For this reason, we conclude that the genotype effect on cognitive ability in Sample 3 may partly be blurred, since both the gf (Rav) and WMC (CSpan) tasks were used to estimate one latent factor. In Sample 4, only reasoning task measures were used to indicate gf, consequently leading to a larger effect size, even though there was less power due to the somewhat smaller size of Sample 4 (N4 = 206) as compared with Sample 3 (N3 = 244). The results of Sample 1, showing differential associations between APOE and various cognitive abilities in terms of effect sizes indicate that genotype differences for WMC and reasoning should be investigated separately. Especially, tasks for memory and mental transformation should be distinguished in future research exploring the association of genetic polymorphisms with cognitive abilities at the latent variable level.

The role of education in cognitive ability

In our analysis of Sample 1 data, latent cognitive performance variables were regressed on both, genotype group and education level, as well as their interaction. For Samples 2, 3 and 4, the interaction model could not be applied because power was not sufficient for the low-education group, especially since there were only few APOE ε4 carriers with low education. In the merged Samples 1 & 2 and 1 & 3, with higher statistical power we were able to separately investigate the ε4 effects on task performance in high and low education groups. Results indicate that the negative APOE ε4 effect found in Sample 1 alone can basically be attributed to lower education level. After controlling for education, there were no overall effects of ε4 on WMC. Thus, negative genotype effects were only present in low education participants. This is in accordance with previous findings (e.g., Arenaza-Urquijo et al., 2015) that better education may help postpone the onset of cognitive impairments among APOE ε4 carriers.

Discussion combining 4.1 and 4.2

The main aim of this Chapter is to investigate the APOE genotype association with brain signal complexity and cognitive ability. Because of limited dataset and measurements, currently we are not able to quantitatively bridge the brain signal complexity and large battery of cognitive ability tasks by the APOE genotype with enough power. For example, the dataset applied in study 4.1 was the combination of sample 3 and 5 in Table 2-1 with identical EEG APOE measurements, while the second dataset applied in Study 4.2, was combination of sample 2 and 3 with same APOE and cognitive measurements, but not EEG recordings. The only possibility to connect APOE, MSE and cognitive performance was using Sample 5 in Table 2-1, but an integrated model connecting these three variables would be much too underpowered with Sample 5. More details will be discussed about the MSE and cognitive performance association induced by Sample 5 in Chapter 5. Here I will only jointly discuss the results of study 4.1 and 4.2 and therefore shed light on the gene-brain-behavior relationship among young adults.

The main conclusion from the APOE-MSE study (4.1) is that 1) APOE ε4 is associated with decreased brain signal complexity at medium and high scale under open eyes condition. 2) APOE ε4 is associated with higher sensitivity of system complexity to external stimulus. The two datasets used in the APOE-MSE study were identical to Sample 2 (combined sample 2 and 3 in Table 2-1) and Sample 4 (Sample 5 in Table 2-1) in the APOE-cognition study (4.2), where APOE ε4 carriers tend to have better cognitive performance. This lead to the

conclusion that less complex high-scale EEG signal and higher dynamic system sensitivity (larger high-scale EO-EC difference) is both associated with better cognitive performance, which are simultaneously detected among young APOE ε4 carriers. According to Mizuno et al. (2010), AD patients who endure serious cognitive decline have significantly increased brain signal complexity as indexed by high-scale MSE. Applying their conclusion to our data may lead to the consistent superiority of low complexity (smaller MSE at high scales) detected among ε4 carriers, who perform better in cognitive tasks.

In case of genotype-brain relationship, the above interpretation is also somehow consistent with the finding that ε4 is associated with reduced complexity among the elder participants (Yang et al., 2013; Cheng et al., 2009). However, decreased complexity detected among elder ε4 carriers (Yang et al., 2013) and increased complexity detected among AD patients (Mizuno et al., 2010) seems to be contradictory to each other. The latter is more introductive to our study since the EEG data were analyzed in similar frequency band, leading to similar definition of low and high temporal scales. However, in case of brain-behavior relationship, our interpretation is contradictory to the review by Garrett et al. (2013) and follow-up studies that higher complexity at high scales (Hager et al., 2016) is related to better cognition performance, where genetic differences were not considered as mediating factor on cognition performance. In Chapter 5 I will mainly focus on the relationship between MSE and cognitive performance, so as to assess my interpretation on the MSE-cognition association with a quantitative model.

Comparing to previous studies on APOE-brain-behavior relationship, the current study filled a knowledge gap about the association of APOE and MSE among young healthy adults, and also added to the literature on the APOE – cognition relationship. The novelty of my study lies in that integrated measurements of both MSE and cognitive behavior was implemented with methodological advancement – Structural Equation Modelling. One limitation of this current study comparing with usual genetic studies is the small sample size. However, we used samples which were possible to be analyzed jointly to maximize the power. Future studies may focus on developing integrated model that connect all the MSE and cognitive performance measurements, so as to provide a complete picture on the early diagnosis of AD for those who are under genetic risk.

5. Neural Process Underlying Face/Object Recognition Characterized by MSE – MSE vs recognition Performance and Single-trial Brain-behaviour Relationship

In Chapter 4, MSE was studied in detail in terms of its potential application as a biomarker for early AD detection. Meanwhile, because of dataset limitation, from an indirect connection, we only literally discussed on possible MSE effects on certain cognitive domain, such as working memory capacity (WMC) and fluid intelligence (gf). There is no unambiguous evidence to validate the direction of the effect among young healthy adults, but we tend to believe that larger resting state MSE at low scale is associated with better cognition performance, while at medium and high scales the direction is opposite under open eyes condition. As mentioned in Chapter 2, MSE as an indicator of base-line brain state and foundation of brain function is predictive for cognitive task performance. In this chapter, with current psychometric recordings we were able to investigate MSE association with another cognitive domain – face/object recognition. Besides the MSE effect on behavioral responses, we further investigated how the underlying neural process of face/object recognition is affected by MSE.

Diffusion model

For binary choice response procedures, a diffusion process has been proposed to decompose the decision process into a series of parameters (Ratcliff, 1978). According to the diffusion model, a stimulus would initiate human brain to accumulate information continuously, rather than discretely, until the information reaches a threshold, or response boundary (a) to drive a response. The corresponding time point when the threshold is reached is the initiation of response. Then after an interval of preparation the response will be executed. The time before threshold reaching can be further divided into two sections. During the first section named non-decision time (*Ter*), no actual information is accumulated, so that this section is not included in the actual decision process. During the second process when information starts to accumulate, a drift rate (v) is used to represent how much information for positive decision was accumulated per unit time (Ratcliff & Rouder, 1998). Above parameters are compositions of EZ diffusion model (Wagenmakers et al., 2007), which was a simplified version of diffusion model. As compared with the complete diffusion model, the EZ diffusion

model could be directly calculated from empirical measured data without necessity of large amount of experimental trials. In this current study in my thesis, the EZ diffusion model, rather than the complete diffusion model will be applied to describe the diffused cognition task related decision making process. A schematic representation of the process described in the diffusion model is given in Figure 5-1.

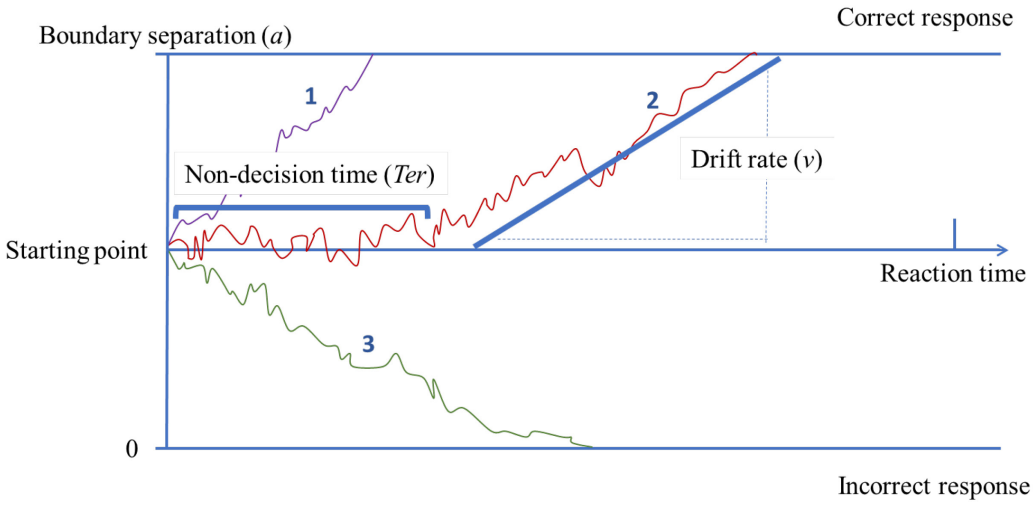

Figure 5-1. Schematic representation of the decision process described by the diffusion model (Adapted from Ratcliff & Rouder, 1998). 1 represents a quick correct response process with high drift rate and without non-decision time. 2 represents a slow correct response process with non-decision time and low drift rate. 3 represents an incorrect response.

According to the concept of a diffusion process, the boundary separation parameter (*a*) represents the amount of accumulated information required to distinguish between the correct and incorrect response. *a* would increase if the participants were devoting more caution in achieving high accuracy. Drift rate (*v*) represents the slope of information accumulation when the decision process starts. Therefore, drift rate is related with the speed of correct responses, with higher drift rate representing improved efficiency of information accumulation. Non-decision time (*Ter*) captures the time needed for task preparation before the onset of the decision process. Small *Ter* parameter lead to faster response speed with equal information accumulation ability. In this study, MSE association with face and object recognition performance was assessed by investigating the MSE effect on the diffusion parameters *a*, *v*, and *Ter* with Structural Equation Modelling.

C (P3) component latency and reaction time correlation

Chapter 1 also discussed the intra-subject variability of ERP and behavioral performance, which could be considered to characterize brain function and cognitive ability above the mean performance. However, the within-person relationship between single-trial ERP and performance is seldom studied. According to RIDE rationale, the C component (P3 component) may capture multiple decision-making related ERP components during cognition task processing which are clustered together (Ouyang et al., 2013). According to well established theory (Kutas et al., 1977), P3 latency is a measurement of stimulus evaluation time, which is independent of response selection and execution time (Figure 5-2). Therefore, relationship between P3/C latency and RT indicates how much reaction time is determined by stimulus evaluation. In another word, reaction time is dependent not only upon the ability of an individual to evaluate information, but also the ability in initiating a motor response. The correlation between C/P3 latency and reaction time represents how much behavior performance speed is contributed by the neural processing of decision making.

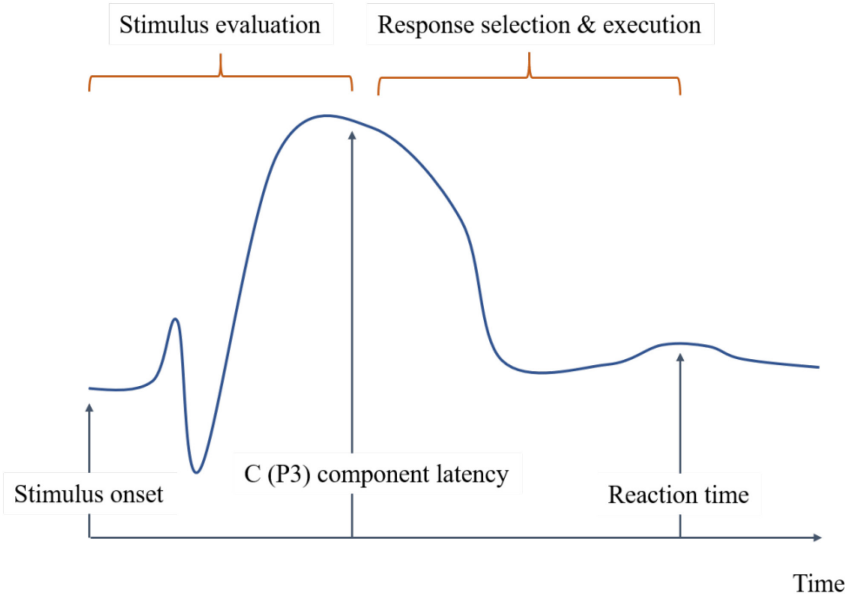

Figure 5-2. Schematic representation of reaction time decomposed by stimulus evaluation and response selection and execution.

Early evidence has validated that the association between P3 latency and reaction time is indicative for brain function. For example, Pfefferbaum et al. (1980) reported a lower association between P3 latency and reaction time in elder person than youngsters, the looser coupling was also accompanied by reduced P3 amplitude and increased P3 latencies and reaction times. The coupling was also lower among patients with depression as compared

with healthy people (Giedke et al., 1981). According to Giedke et al. (1981), the lower processing speed and longer reaction time, the more vulnerable the brain system to be disrupted by the distractor to perform motor response, which means less correlation between P3 latency and reaction time. Therefore, if the correlation is high, then behavioral performance is highly defined by stimulus evaluation, we may expect a more functional brain system with faster reaction speed.

The current study is interested in 1) whether MSE characterizes behavior performance in face/cognition task and 2) whether the correlation between C/P3 latency and reaction time is also dependent on brain signal complexity measured by MSE. By investigating these two questions, we want to know how MSE could characterize brain function from different aspects. The results will be displayed in two separate sections: MSE association with face and object recognition task performance and MSE association with C latency – RT correlation.

Samples and measurements

The sample used for the current study is described in sample section of Chapter 2, sample 5. As described there, both EEG and psychometric records were contained in this sample. The EEG session includes 90s of closed eyes resting state recording and 90s of open eyes resting state recording, as well as 72 trials * 16 conditions recording ERP under face and house recognition tasks. Moreover, the participants further took an independent face and object psychometric task session which was independent of the EEG session. Task measurements of EEG and psychometric is described in Table 5-1. Abbreviation of measurements and parameters computed from the EEG and psychometric session is summarized in Table 5-1 after data processing and treatment. Detailed description of the abbreviation of the task measurements will be given in section 5.1.

Table 5-1. Measurements and parameters obtained for each participant

EEG session		
Resting state EC	Resting state EO	Task
MSE * 4	MSE * 4	1. MSE * 16 conditions

session	session	2. RIDE C latency *16 conditions * 72 trials

Psychometric session									
OMS	OPS	FMS	FPS	FMA 1	FMA 2	FMA3	OMA1	OMA2	OMA3
a, v, Ter	*a, v, Ter*	*a, v, Ter*	*a, v, Ter*	acc	acc	acc	acc	acc	acc

5.1 MSE association with recognition task diffusion parameter

In this session, I will use SEM to investigate the association between MSE and diffusion parameters of the face/house cognition tasks, so as to assess MSE effect on performance at different task processing stage. The diffusion parameters were derived from the psychometric task session in Table 1; MSE were derived from the resting closed and open eyes and task EEG session in Table 5-1.

Task EEG measurements and data treatment

The EEG experiment consisted of 16 conditions that differed in content domain (face vs house stimuli), difficulty (speed task vs. accuracy task), familiarity (familiar vs unfamiliar stimuli) and priming (primed vs unprimed stimuli). Since the condition differences are not investigated in the current study, I will skip the detailed description of each condition. Each condition included 72 single experimental trials. During each trial, participants first saw a cross for fixation lasting for 1000 ms, followed by a prime stimulus presented for 500 ms. Then the stimulus was replaced by a circle fixation for 1300 ms, and finally a target stimulus presented for 2000 ms. For each condition and each participant, RIDE was applied to obtain all the reconstructed ERP and C component latencies for all single trials, so that for all participants, C component latencies of 72* 16 experimental trials as well as their corresponding reaction times were obtained for further modelling.

Psychometric task measurements and data treatments

The psychometric session also included general object recognition and specific face recognition. Participants were instructed to respond as fast and accurate as possible. These

psychometric tasks include speed (easy) tasks and accuracy (difficult) tasks. Because of different difficulty, the speed and accuracy measurements were from different tasks. The time used from stimulus to responding of speed tasks were recorded as reaction time (speed), and the probability of correct response was recorded as accuracy of the accuracy task. A brief description of all the tasks regarding to Table 5-1 is given below.

Stimulus matching of morphed faces (FPS) and houses (OPS). These two are speed tasks. Each trial included two different morphed faces or houses which were generated from the same two original face or house images. Participants were asked to decide whether the two morphed images were similar or not. Similar faces or houses were generated from 50% of both original images, while non-similar stimulus was generated from 20% of the first original image and 80% of the second image. Participants needed to take 320 trials in total, and their reaction time and accuracy of each trial were recorded.

Delayed nonmatching to sample with faces (FMS) and houses (OMS). These two are speed tasks. Image of a face or house was presented. Then the identical image together with a new image of the same kind were presented, with the new image presented on the left or right (50% - 50%) side of the old image. Participants were asked to tell whether the new image was presented on the left- or right-hand side of the old image. 92 trials in total were performed with their reaction time and response accuracy recorded.

Learning and recognition of faces (FMA1) and houses (OMA1). These two are accuracy tasks. A learning phase was first performed. Participants needed to remember as many of 30 faces or house stimuli as possible within 45s; all stimuli of a given learning phase were positioned within matrices shown on the screen. Thereafter, the stimuli to be memorized were presented next to a new face or house stimulus in sequence. Each of the memorized images was presented three times, each time with a different new image alongside. 90 pairs of stimuli were presented in total during the whole recognition phase. Reaction time and correctness of each response were recorded.

Decay rate of learned faces (FMA2) and houses (OMA2). 90 minutes after the previous learning and recognition phase, a second block of learned and unlearned face and house images were presented in sequence without extra learning phase. In this block, participants were required to decide whether the face or house image had been previously learned. These two are accuracy tasks.

Eyewitness testimony of faces (FMA3) and houses (OMA3). Similar to the previous tasks, participants were asked to identify the familiar stimulus from a stimulus pair. But this time the familiar stimulus was used in a different task phase rather than the learning phase in this session, so that participants needed to identify them without being instructed to specifically memorize them. During this task, 45 stimulus pairs were presented in sequence to each participant. These two are accuracy tasks.

After recording reaction time and accuracy (proportion of correct response for each task) of these psychometric tasks, within-subject RT outliers (reaction time below 200ms) as well as Tukey outliers (Tukey, 1977) were excluded. The diffusion model parameters for each individual were calculated by applying R code provided by Wagenmakers et al. (2007). RTs, variances of RTs and response accuracies were used for calculating the boundary separation (*a*), drift rate (*v*) and non-decision time (*Ter*). The calculation was implemented by my colleagues (Meyer et al., 2019) and I am using the available parameters with their consent for further modelling.

Descriptive information on the RT description and diffusion model parameters

In order to justify the application of EZ diffusion model on the stimulus-matching face and object cognition task, the distribution of RT and calculated diffusion parameters are displayed in Table 5-2. As is shown in the table, more difficult task (FPS and OPS) as defined by large mean RT and larger across-subject standard deviation are characterized by lower drift rate, longer non-decision time and more conservative boundary separation.

Table 5-2 Mean values (Between-person standard deviation) of intra-individual RT means (M), RT standard deviations (SD), RT accuracies (Accuracy), EZ-diffusion parameters (*a*, *v*, *Ter*) for each speed tasks

Speed task	*M*	*SD*	Accuracy	*a*	*v*	*Ter*
FPS	1350 (435)	492 (306)	.87 (.08)	5.66(1.95)	.003 (.001)	698 (144)
OPS	1327 (396)	419 (240)	.95 (.05)	6.44(2.12)	.005 (.001)	723 (131)
FMS	1005 (390)	275 (200)	.94 (.11)	5.61(2.87)	.004 (.002)	369 (521)

OMS	1012 (377)	314 (163)	.95 (.08)	6.11(1.85)	.006 (.001)	536 (174)

Measurement model for MSE and psychometrics

Unlike the MSE study in Chapter 4.1, in the current study only one dataset with sample size of 190 was available for modelling MSE and psychometric performance relationship. In order to keep sample size as large as possible, MSE was calculated following Kaur et al. (2019), where each MSE segment indicators included 2500 data points (10s EEG recording). According to Kaur et al. (2019), the reliability of MSE computed basing on this data length was acceptable until scale 10 (above .50). Therefore, following the same grouping of MSE scales as described in Chapter 4, we grouped scale 1-4 MSE as low scales and 5-10 as medium scales, and calculated low and medium scale AUC scores accordingly. Unlike Chapter 4 where MSE calculated from only resting state EEG was included, the current study included EEG that has been collected during a task as well as during rest. In the MSE measurement model, the latent variable of closed and open eyes MSE was indicated by the four segment indicators, while the latent variable of task MSE was indicated by the 16 condition indicators, each of the condition indicators averaged across 4 segment indicators. The measurement models have already been investigated by Kaur et al. (2019), where a latent factor representing the unfamiliarity specific stimulus was nested under the general task MSE (details of the model was given in Figure 5-3 below), which means that MSE measured under unfamiliar tasks was distinct from MSE measured generally under all tasks.

Psychometric performance in the current study was modeled as 4 different latent factors with available data: the diffusion model parameters *a*, *v* and *Ter*, as well as performance accuracy. The *a*, *v*, and *Ter* parameter factors were indicated by *a*, *v*, and *Ter* parameters calculated from 4 speed (easy) task performance: OMS, OPS, FMS and FPS (Table 5-1). The accuracy factor was indicated by six accuracy (difficult) task accuracies: FMA1, FMA2, FMA3, OMA1, OMA2 and OMA3 (Table 5-1). Confirmatory factor analysis (CFA) suggested that these measurement model fittings were quite good, so that the proposed latent factors could well account for the isomorphism among these indicators.

MSE association with task performance

Structural equation modelling was applied to investigate whether psychometric performance could be predicted by latent variable of MSE for low and medium scale AUC under resting

state closed and open eyes, as well as during task. For each condition, we use Fz and Pz as representative electrodes to present the MSE-performance association at frontal and parietal scalp. Figure 5-3 gave representation of SEM exploring the MSE effect on diffusion model parameters. The same model as described in Figure 5-3 was separately applied on *a*, *v* and *Ter* parameters. Figure 5-4 shows how MSE might affect accuracy of the accuracy (difficult) task performance. The model results are given in Table 5-3. All regression coefficients were standardized, so that the magnitude of effects is between 0 and 1.

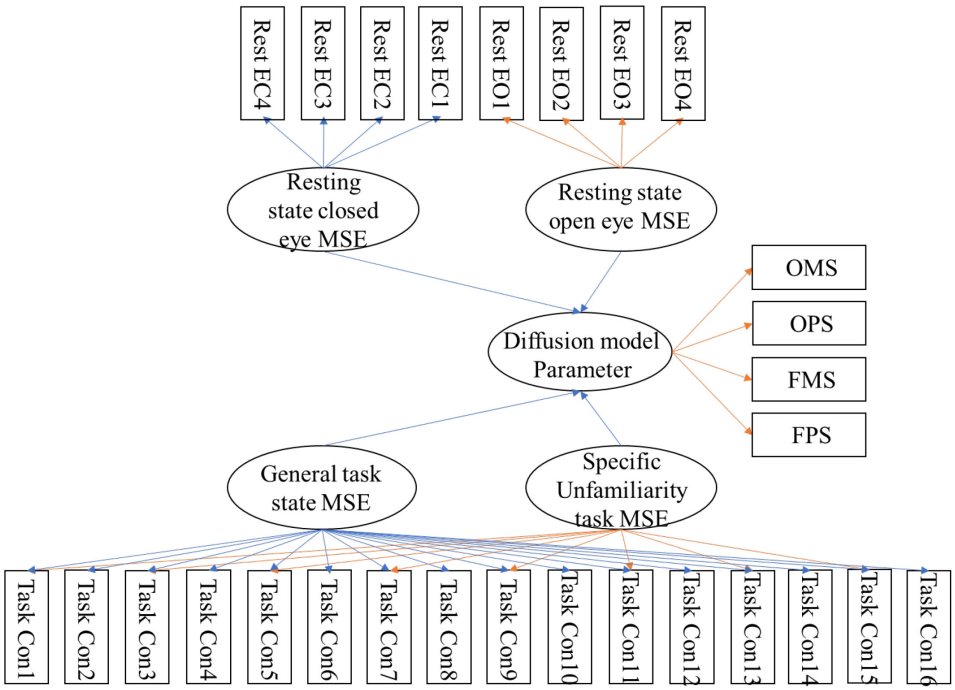

Figure 5-3. Schematic representation of Structural Equation Model investigating resting state and task state MSE association with diffusion model parameters. FPS - stimulus matching of morphed faces; OPS - stimulus matching of morphed houses; FMS - delayed nonmatching to sample with faces; FPS - delayed nonmatching to sample with houses; Rest EC 1-4 – resting state eyes closed MSE calculated from EEG session 1-4; Rest EO 1-4 – resting state eyes open MSE calculated from EEG session 1-4; Task Con 1-16 – task MSE calculated from task EEG under condition 1-16.

Table 5-3 presents model result of MSE effect on response caution (*a*). Results indicated no consistent effect of eyes closed or task MSE on response caution.

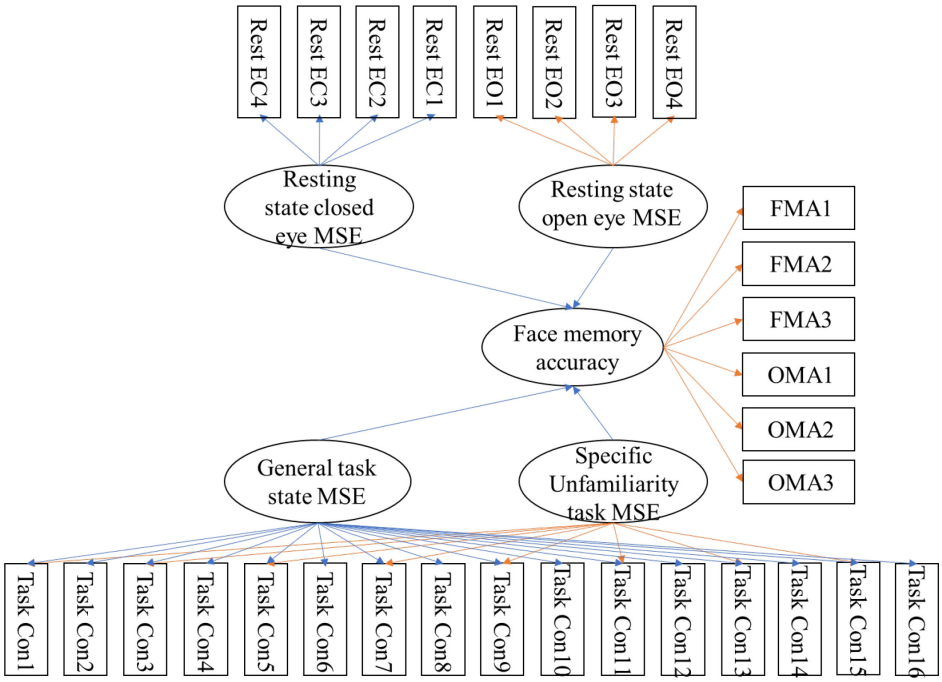

Figure 5-4. Schematic representation of Structural Equation Model investigating resting state and task state MSE association with face/object recognition task performance accuracy. FMA 1-3: face accuracy task 1-3; OMA 1-3: house accuracy task 1-3; Rest EC 1-4 – resting state eyes closed MSE calculated from EEG session 1-4; Rest EO 1-4 – resting state eyes open MSE calculated from EEG session 1-4; Task Con 1-16 – task MSE calculated from task EEG under condition 1-16.

Table 5-3. MSE AUC under resting state and task conditions association with diffusion model parameter *a*

Electrode	Temporal scale	Regression weights			
		MSE_{EC}	MSE_{EO}	MSE_{GTask}	MSE_{Unfam}
Fz	Low scale	-.02	-.14	.03	-.04
	Medium scale	-.03	-.16	.01	.16
Pz	Low scale	-.02	-.14	.07	-.16
	Medium scale	-.03	-.12	-.01	-.02

Note: MSE_{EC} – eyes closed MSE AUC; MSE_{EO} – eyes closed MSE AUC; MSE_{GTask} – general task MSE AUC; MSE_{Unfam} – unfamiliar task specific MSE. * : *p*-value <.05.

Table 5-4. MSE AUC under resting state and task conditions association with diffusion model parameter *v*

Electrode	Temporal scale	Regression weights			
		MSE_{EC}	MSE_{EO}	MSE_{GTask}	MSE_{Unfam}
Fz	Low scale	.22*	-.03	.18*	-.06
	Medium scale	.28*	-.04	.13	-.10
Pz	Low scale	.24*	-.04	.08	-.07
	Medium scale	.27*	-.04	.03	.04

Note: MSE_{EC} – eyes closed MSE AUC; MSE_{EO} – eyes closed MSE AUC; MSE_{GTask} – general task MSE AUC; MSE_{Unfam} – unfamiliar task specific MSE. * : *p*-value <.05.

Table 5-4 shows MSE effects on the diffusion model parameter *v*, that is, drift rate. As indicated by the result, MSE measured under closed eyes resting state has consistent positive effect at all the scales. This means that the higher MSE (when eyes are closed), the faster people could make correct responses (under the same boundary separation). In another words, the higher MSE of a person during closed eyes resting state, the faster is information accumulation during a task situation. MSE measured under general task condition has the same effect direction on drift rate, but not consistently significant. Under open eyes and unfamiliar specific task condition, there is no association of MSE with drift rate.

Table 5-5. MSE AUC under resting state and task conditions association with diffusion model parameter *Ter*

Electrode	Temporal scale	Regression weights			
		MSE_{EC}	MSE_{EO}	MSE_{GTask}	MSE_{Unfam}
Fz	Low scale	-.30*	.02	.00	-.15
	Medium scale	-.32*	-.02	.04	-.18

Pz	Low scale	-.30*	.02	.08	-.20
	Medium scale	-.33*	.00	.03	-.15

Note: MSE_{EC} – eyes closed MSE AUC; MSE_{EO} – eyes closed MSE AUC; MSE_{GTask} – general task MSE AUC; MSE_{Unfam} – unfamiliar task specific MSE. * : *p*-value <.05.

Table 5-5 gives results of MSE effect on the non-decision time (*Ter*). According to the results, MSE measured under closed eyes resting state at both low and medium scale is negatively related to non-decision time (*Ter*). Under unfamiliar specific task condition, the effect also has a negative trend, but not significant. This means that increased MSE measured under both these two conditions is associated with decrease in task preparation time, which does not count for the time used for information accumulation. In another word, if a person has higher MSE during closed eyes resting state, this person will have more energy utilized for actual information accumulation, but less waste of time in preparing process and stimulus encoding (Schmitz & Voss, 2012, 2014; Ratcliff & Tuerlinckx, 2002; Voss et al., 2004).

Table 5-6. MSE AUC under resting state and task conditions association with face/object memory accuracy

Electrode	Temporal scale	Regression weights			
		MSE_{EC}	MSE_{EO}	MSE_{GTask}	MSE_{Unfam}
Fz	Low scale	.26*	-.02	.01	.15
	Medium scale	.21*	-.05	-.16	.26*
Pz	Low scale	.24*	-.01	.07	.01
	Medium scale	.21*	-.05	-.11	.06

Note: MSE_{EC} – eyes closed MSE AUC; MSE_{EO} – eyes closed MSE AUC; MSE_{GTask} – general task MSE AUC; MSE_{Unfam} – unfamiliar task specific MSE. *: *p*-value <.05.

Table 5-6 gives results of MSE association with task performance accuracies. According to the results, higher MSE under eyes closed resting state was correlated with higher

performance accuracy. However, under eyes open resting state and task state there was no correlation.

To sum up, in terms of face/object recognition domain, increased MSE is associated with improved task performance. The superiority could be detected from both speed and accuracy of task performances, while the speed performance was induced by the diffusion model parameter of the easy tasks and the accuracy performance was induced by the correct response rate of the difficult tasks. These improvements in task performance include increased drift rate and decreased non-decision time in diffusion process, as well as increased accuracy of task performance. All of these individual differences in task performances were significantly predicted by MSE measured under resting state closed eyes condition, when brain activity was spontaneous without any external stimulus, and, therefore, could be regarded as personal trait irrelevant to environmental change.

5.2 MSE association with C latency – RT correlation

As introduced in Chapter 1, intra-subject variabilities at both neurophysiological and behavioral levels have been well recognized and established as a personal trait. By applying RIDE method, the single trial ERP C component can be obtained, which has been well proved to capture central-processing process (Ouyang et al., 2011), and therefore captures the quickness of decision making process. This section is interested in the relationship between C latency and reaction time (RT), and how the relationship is modulated by MSE measured at resting state. Investigating this question is based on multilevel data modelling.

Multilevel data structure

Multilevel data refers to data structure with records clustered in *J* groups. In our study, the two levels are within-subject and between subject level. Recordings acquired at within-subject level include signal-trial C component latency and single trial reaction time, while each subject has multiple repeated recordings. Between-subject recordings include all the MSE measurements and each subject have only one recording. Figure 5-5 gives an overview of all the C latency and reaction time recordings of all subjects. Each subject has a regression line with different slopes. Each regression line was plotted basing on the 16*72 trials of C latency and reaction time recording. In this figure, most of the C latency values are between -300 and 300, because RIDE algorithm provide C latency values computed as time lag of each single

trial C latency comparing to the individual specific ERP template peak latency (see RIDE algorithm description is Chapter 2). It can be visually detected from Figure 5-5 that reaction time can be predicted by C latency. According to interpretation by Kutas et al. (1977), this means that reaction time could be predicted by stimulus evaluation, and the predictability (regression line slope) is variable across individuals.

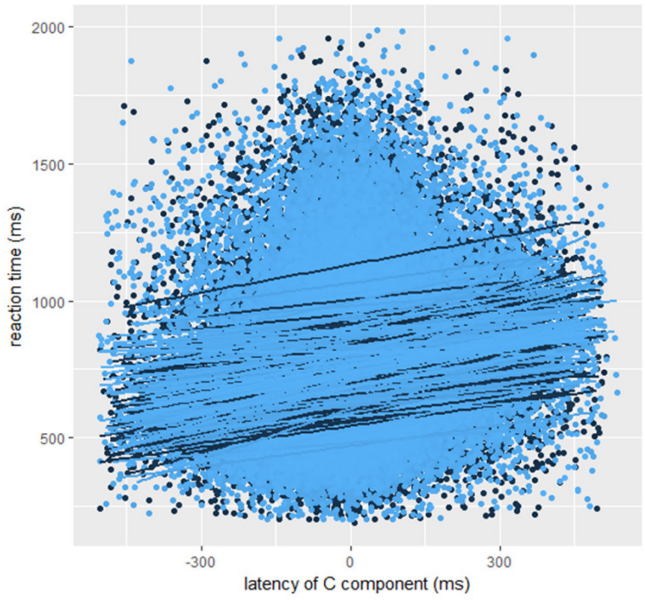

Figure 5-5. Relationships between C component latency and reaction time for all individuals. Data points and regression lines with different colors represents different subjects.

Random effect model (Two level SEM)

Random effect model is widely applied for investigating relationship between multilevel data structure. In our case, the observed within-subject level response, RT, is supposed to follow normal distribution. The *i*th RT observation of the *j*th subject can be referred to as y_{ij}. Correspondingly, the within-subject level predictor, C latency is referred to as x_{ij}. The variance of RT could be decomposed into two parts: between subject variance which represents variation across individuals, and within subject variance, which represents variation in measurements acquired within subjects. Relationship between y_{ij} and x_{ij} can therefore be represented as follows:

$$y_{ij} = r_{00} + r_{10}x_{ij} + \mu_{0j} + \mu_{1j}x_{ij} + e_{ij}$$

or

$$y_{ij} = \beta_{0j} + \beta_{1j}x_{ij} + e_{ij}$$

where the intercept $\beta_{0j} = r_{00} + \mu_{0j}$, and the slope $\beta_{1j} = r_{10} + \mu_{1j}$.

As indicated by the formulas, both the intercept and slope are composed by fixed effect (r_{00} and r_{10}) which does not vary across individuals and random effect, which is different across individuals (μ_{0j} and μ_{1j}). Fixed intercept r_{00} represent for the grand intercept of all the reaction time measures and random intercept μ_{0j} represent for the intercept of the *j*th subject. Fixed slope (r_{10}) represent for the common effect of C latency on reaction time for all individuals. As described in Figure 6, the slope is variable across individuals, which is referred to as random slope. This study is interested in whether individual difference in resting state MSE is part of source of variations in β_{0j} and β_{1j}.

Figure 5-6 described the random effect model that investigating the MSE association with the within-subject slope. Note that here RTs and C latencies were recorded from the same experimental trials, and the MSE was from a different condition from RT and C latency recordings. Same as 5.1, only low and medium scale MSE was applicable. The upper part describes the within subject relationship between C latency and reaction time. The lower part describes the between-subject relationship between the latent variable of MSE on the within-subject slope. The latent variable of MSE eyes closed and eyes open were indicated by 4 MSE AUC indicators. The model depicted in Figure 5-6 was applied on Fz and Pz channel as representative channel for frontal and parietal scalp. The result was displayed in Table 5-6.

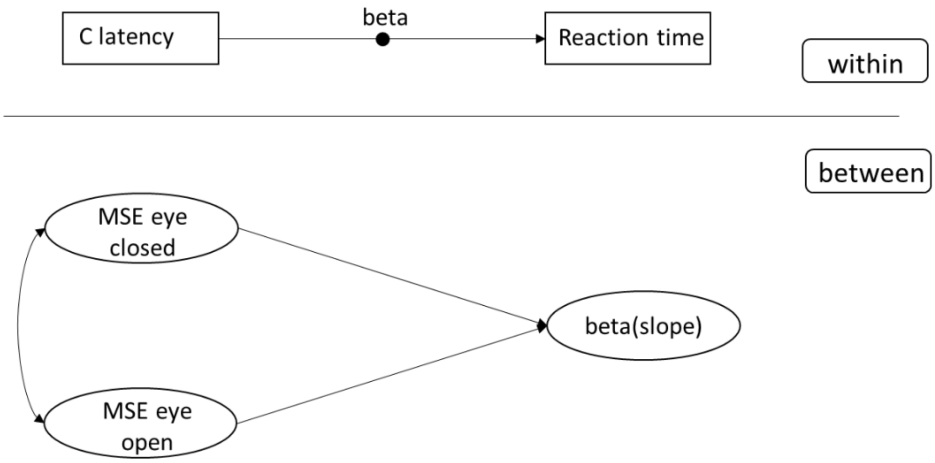

Figure 5-6. Schematic representation of random effect model exploring the association of between-person-level MSE with brain-behavior relationships at within-person level.

Table 5-7. Association of MSE under resting state conditions with random slope of C latency and RT relationship

		Regression weights on random slope	
		MSE_{EC}	MSE_{EO}
Fz	Low scale AUC	-.01	-.02
	Medium scale AUC	.04*	-.01
Pz	Low scale AUC	-.04*	-.02
	Medium scale AUC	.01	-.01

As indicated by Table 5-7, there is generally no consistent MSE AUC association with the random slope of the C latency and RT relationship. However, the direction of the effect showed that under closed eyes condition, MSE effect on the random slope is negative at low scale at electrode Pz and positive at high scale at electrode Fz, while under open eyes condition, the MSE effect is always in negative direction. As an exploration, we further investigate scale-specific MSE association with C latency and RT relationship.

Figure 5-7 displays the scale-specific MSE association with the random slope, that is, the random slope was regressed on MSE estimated at each scale 1-10 separately rather than integrated low (1-4) and medium (5-10) scales. For example, in the left panel, MSE association at scale 8 Pz channel on random slope is around 0.4, meaning that 1 unit increase in the scale 8 MSE value at scale 8 would lead to around 0.4 unit increase in the C latency – RT regression parameter. As shown in Figure 5-7, under both closed eyes and open eyes condition the MSE association was non-significant at lower scales. However, the association was significant for scale 7 and 8 under both closed and open eyes condition. The direction association was positive under closed eyes condition and negative under open eyes condition. As compared with AUC measurement in Table 5-7, the scale-specific MSE association with the C latency - RT slope was more consistent at scale 7 and 8. It is possibly the association was smeared up when averaged across several scales, while the associations at other scales are

not significant. Therefore, rather than applying an integrated MSE measure such AUC, we choose single scale 7 and 8 MSE to measure the association with C latency and RT slope.

Figure 5-8 showed the difference in direction of MSE effect at higher scales. As is discussed in Chapter 4.1, the difference in MSE measured under EO and EC condition indicate the flexibility of dynamical brain system. According to Figure 5-8, we assume that the difference between EO and EC MSE may also be related with the

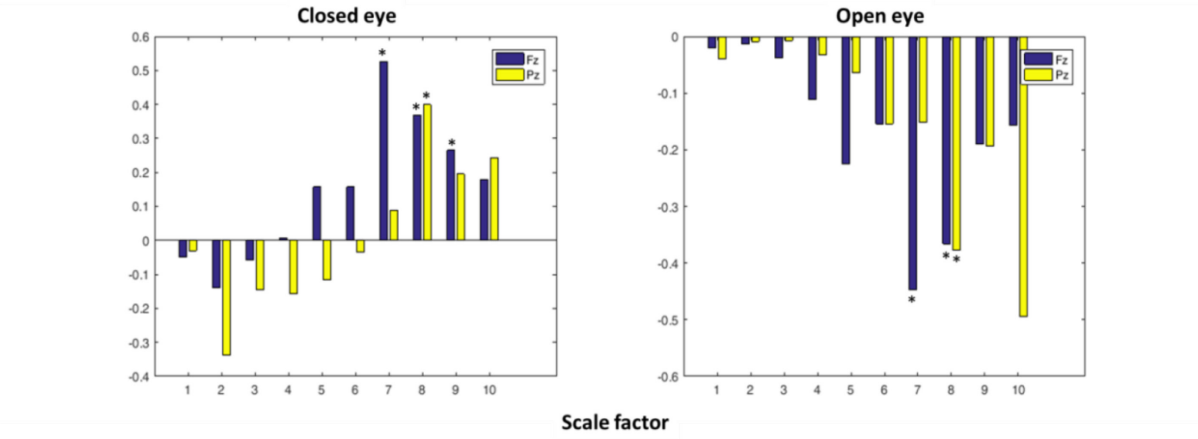

Figure 5-7. Regression coefficient of MSE association with the random slope of C latency and reaction time relationship. *: *p*-value < .05.

C latency and reaction time relationship. We use MSE measured under scale 8 as a representation to investigate its difference effect on the slope. Figure 5-8 depicts the latent difference score modelling of the association on Fz channel. Model result indicated that the estimated mean of MSE latent difference was -.12 and was negatively related to the slope.

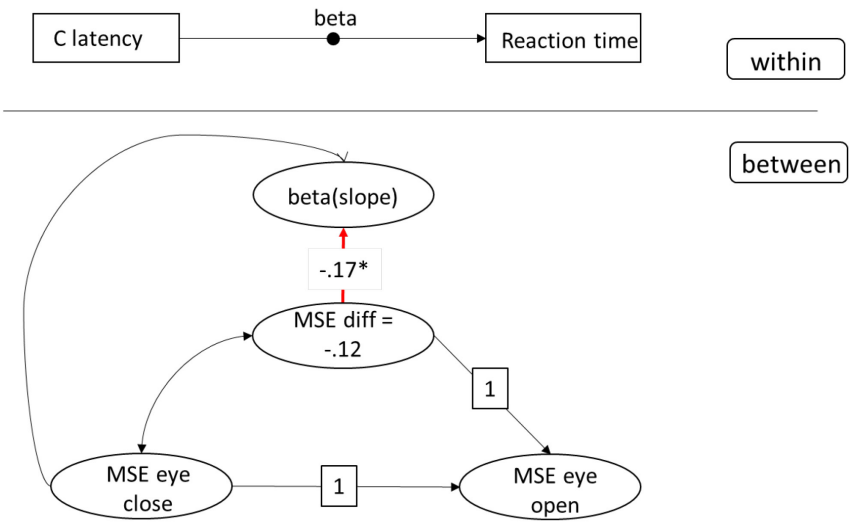

Figure 5-8. Schematic representation of structural equation model exploring the difference Fz channel eyes open – eyes closed MSE association with the random slope of C latency-reaction time relationship.

To summarize, MSE measured under both closed and open eyes resting state, which reflect the ongoing complexity of brain signal, may be related to the underlying neural process during face/house recognition tasks, and the relationship is especially pronounced at medium scales (scale 7 and 8). From the view of individual difference, in could be interpreted as: under closed eyes condition, those individuals with higher MSE measured brain signal complexity as a personal trait, also have tighter dependence of RT on C latency (larger slope), whilst under open eyes condition, they will have more loose dependency. The MSE difference model suggested negative relationship between MSE eyes open – eyes closed difference and random slope. This means that those individuals with large absolute MSE difference will also have high the random slope. In another word, when people open their eyes, the brain signal will decrease because of external stimulus. The larger decrease, the higher dependency of reaction time on the stimulus evaluation process is.

5.3 Combined discussion

This Chapter investigated how MSE characterize the performance of face/object recognition as well as the underlying neural processing. The results could be summarized as follows: 1) At behavior level, individuals with increased MSE measured under resting state closed eyes condition will have better cognitive performance. The effect could be detected from several facets. Firstly, increased MSE is correlated with reduced time necessary for preparation of information accumulation to make correct response. Secondly, once the information starts to accumulate towards correct response, increased MSE is associated with higher accumulation velocity. Thirdly, increased MSE is correlated with higher probability for making correct response. 2) At the neural processing level, MSE measured at higher scale may be related with the dependency of motor response on stimulus evaluation process. If the higher scale MSE drop from closed to open eyes condition is larger, then the motor response is more tightly dependent on the central evaluation process. To sum up, increased MSE is association with improvement in brain function.

MSE and cognitive performance

We conducted diffusion model to decompose the reaction time and therefore interpret the individual difference in speed and accuracy of the cognition performance in the diffusion parameters. The decomposed parameters provide insight for quantifying cognitive ability in different processing stages. Therefore, the novelty of the current study is to investigate MSE effect on cognitive ability dissolved into different process, so as to investigate the crucial process modulated by MSE. This is the first study which directly investigated the MSE association with cognition performance in the perspective of diffusion process, even though the diffusion model parameters have been successfully applied to assessing individual difference in reaction time caused by aging and mental disorders (e.g., White et al., 2010; Ratcliff et al., 2006). Results showed that individuals with increased MSE will have higher drift rate and reduced non-decision time, which lead to faster speed to make correct response. Moreover, accuracy is increased among high-MSE subject. All of these results were only consistent under closed eyes resting state, while the brain activity is completely spontaneous and the MSE measurement could be more reliable for evaluating ongoing brain activities without visual inputs from environment. This is in accordance with the mainstream point of view that higher MSE is associated with better performance (e.g., McIntosh et al., 2008).

The predictiveness of P3 latency for RT within the same trials has been investigated in a previous study by Rostami et al. (2017). In different study samples, Rostami et al. (2017) showed that the dependency of RT on C latency was stronger among homozygotes of Val gene allele as compared with Met homozygotes, but the trial-to-trial C latency variability was weaker. Moreover, the predictability under familiar condition outperforms the unfamiliar condition. These results point to the conclusion that higher predictability of C latency on RT is associated with more stable neural processing and less demanding in decision making speed.

However, the psychophysiological meaning of C latency predictability on reaction time was not explicitly interpreted by Rostami et al. (2017). Our result on several higher MSE scale suggested that under closed eyes condition, MSE increase leads to the predictability increase, while under open eyes condition, the effect was opposite. If we only focus on the closed eyes condition, higher brain complexity characterize those individuals whose behavior are more tightly coupled to stimulus evaluation. This tight coupling therefore leads to stronger reduction in brain signal complexity when they open their eyes and novel input comes.

Comparison with Chapter 4 result

Even though results from face and object cognition tasks lead to the conclusion that larger MSE at medium scale (scale 7-8) is associated with increased brain function and better cognitive performance, this may not always be the case when coming to different task batteries. Chapter 4 discussed the relationship between APOE ε4 and working memory/reasoning, as well as APOE ε4 and MSE, but the MSE association with working memory / reasoning was not systematically explored. Therefore, we applied SEM to investigate MSE association with the same measurement of reasoning task accuracy as Chapter 4.2 (sample 4), so that MSE under closed eyes, open eyes and task conditions was separately regressed on reasoning. The results are displayed in Table 5-8, which indicated that there was actually no MSE effect on reasoning task performance under any condition. Therefore, the association of MSE and cognitive ability should be largely dependent on the task domain. In fact, various studies have validated the distinction between face and object recognition ability and intelligence (Richler, Wilmer, &Gauthier, 2017; Shakeshaft & Plomin, 2015). On the other hand, as a more general cognition domain than face and object recognition, modulation of reasoning ability may be attributed to more global brain areas, rather than singly recorded from two EEG electrodes. Therefore, MSE calculated from further neuroimage technique such as fMRI recording with higher spatial resolution could be applied to better interpret the brain signal complexity association with reasoning ability.

Table 5-8. Association of MSE under resting state and task conditions with reasoning

Electrode	Temporal scale	Regression weights			
		MSE_{EC}	MSE_{EO}	MSE_{GTask}	MSE_{Unfam}
Fz	Low scale	.04	.09	-.11	-.06
	High scale	.04	.11	-.03	.13
Pz	Low scale	.04	.03	-.05	-.03
	High scale	.06	.07	.09	.00

Note: MSE_{EC} – eyes closed MSE AUC; MSE_{EO} – eyes closed MSE AUC; MSE_{GTask} – general task MSE AUC; MSE_{Unfam} – unfamiliar task specific MSE. *: *p*-value <.05.

Limitation of the current study

The present study extended our knowledge on MSE and cognitive ability to the diffusion process and decision-making procedure. However, it is noticeable that the MSE effect was not consistently significant for all conditions and temporal scales, especially that MSE effect on C latency and RT slope was only significant for one or two scales, even though a trend in effect size change could be observed across scales (Fig. 5-8). We can only interpret the significant effect as a sensitivity in dynamic states, but the effect across scales was not clear yet. On the other hand, the application of AUC measure when investigating the MSE and C latency – RT slope failed to increase the association significance, possibly the association was smeared up when averaged across several scales. Therefore, we should cautiously apply MSE AUC score as an integrated measure of MSE.

Secondly, this current study did not consider experimental effect (conditional difference) which has been reported to link with both diffusion process (Ratcliff & Childers, 2015) and C latency (Rostami et al., 2017). One probable reason that the MSE effect was not consistent across scales might be the smeared effect when experimental conditions were averaged. One future direction to improve the current study could be exploring for more cautious modeling that takes into account for the experimental conditional effects.

6. General Discussion and Outlook

6.1 Summary of findings

The main goal of my doctoral study was to contribute with deeper understanding in brain signal complexity, its genetic determinate and its influence on dispositional cognitive abilities. The brain signal complexity was measured by Multiscale Entropy (MSE), which is a widely used approach to quantify complexity of brain signal time series. The cognitive ability was assessed from two facets: the face and object cognition and working memory/reasoning ability. The genetic determinant factor was APOE ε4, which was a well-known genetic risk factor for Alzheimer Disease, and therefore probably also associated with cognitive performance among young adult people. When investigating the MSE association with cognitive performance, ERP was used for indicating the cognition process at neural level. However, since traditional ERP analysis method brings up smearing problem on ERP components when multiple trials were averaged due to trial-by-trial latency variability, RIDE method was applied to overcome this weakness.

In Chapter 3, we first applied RIDE method on a dataset that was independent of the main topic of the current thesis as a validation of the methodological advancement. The result of this Chapter confirmed that the application of RIDE will increase the sensitivity of ERP change to the experimental condition alteration, because the smearing effect of conventional ERP analysis was reduced. In Chapter 4, the individual difference in relationship between APOE and MSE, as well as the relationship between APOE and working memory were assessed. Chapter 4 concluded that APOE ε4 association with working memory capacity could be complex across population with different education levels. Generally, APOE ε4 carriers will deteriorate the working memory/reasoning performance among the less educated persons, but the effect might be attenuated or even slightly inversed among the high educated people. Using the same dataset that exhibit slightly but non-significant superior working memory performance among APOE ε4 carriers, the MSE of APOE ε4 carriers were found to be higher at small scale and lower at large scale. However, caution should be taken against over-interpretation of the association between reduced complexity (indicated by decreased large scale MSE) and better cognitive performance in varied cognitive domain. In Chapter 5 we specifically investigated the relationship between MSE and face/object cognition

performance. Result indicated that for the face/object cognition domain, MSE is positively related with the cognitive performance in terms of the diffusion process of reaction time, as well as the sensitivity of behavior response to the stimulus evaluation at the neural level.

Chapter 4 and 5 were two highly linked chapters which aim for the investigation of gene-brain-behavior, basing on the general assumption that the manifested impact of gene on cognition behavior was intervened by the modulation of underlying brain activity. For the gene-behavior association, mixed result was demonstrated, but basing on more reliable statistical methodology as compared with previous studies. For the gene-brain association, we find that APOE ε4 allele was associated with decreased brain signal complexity especially at open eyes condition, while higher level of brain sensitivity. These results may contribute for the establishment of potential biomarker for early AD detection. For the brain-behavior relationship, we generally found increased brain signal complexity under closed eyes condition is associated with better cognitive ability.

6.2 limitations and future work

Even though the individual difference in relationship between APOE genotype, MSE and cognitive performance was extensively discussed in my doctoral study, there are some limitations that should be improved in future studies. The limitations are summarized as follows.

Limited sample size was one of the main shortcomings in each of the studies, especially in Chapter 4 and 5. Advanced genetic studies for genome-wide association usually need very lager sample size to address the single nucleotide polymorphism (SNP) association with phenotypes. For example, Nishino et al. (2018) suggested notable increase in depression-associated SNP only when over 50000 cases with depression disorder were collected. Therefore, our study on the APOE – working memory and MSE associations with complicated modelling method would be definitely underpowered. This could partly contribute to the insignificant result across several study samples.

Inconsistent result such as the mixed effect direction of gene-behavior study in Chapter 4.2 may also be attributed from varied potential factors playing interaction effect on working memory performance which was ignored in the current study. For example, there's large age range within each sample (between 20 - 40), which could largely account for the performance

difference. The distribution of APOE genotype was also not balanced across samples. In sample 3 there's much higher proportion of APOE ε4 carriers as compared with other samples, which probably also strengthen the genome effect than other samples.

Another limitation emphasized in Chapters 4 and 5 was that even though we tried to combine samples where applicable to increase the power, there was lack of integrate model that combine the APOE genotype, MSE and cognitive performance together. This is because the sample with both EEG recording, APOE genotype and appropriate working memory capacity measurement has only size of around 70 (Sample 3). This sample size is too small for the construction of latent variable analysis to account for the measurement errors. However, it would be of great interest to construct model that directly bridge the multiple indicators of these three measurements. One of our future study aims would be the investigation of the mediation of brain activity on the gene-behavior association, which should be based on better-designed data collecting and analysis scheme and statistical power analysis.

Even though the face and object cognition tasks applied in Chapter 5 was performed under different conditions, the conditional difference was not taken into consider in the analysis of my thesis, which is another limitation that should be noticed in future analysis. Since the accuracies of face cognition performance was suggested to be specific from object cognition (Rostami et al., 2017), future study may treat face cognition task performance as a particular variable which is related with MSE measurement. Probably the face cognition task performance and its association with MSE estimated both under resting state and specifically under face cognition task could be extensively studied to address the brain signal complexity effect on structural encoding of face stimulus.

Another difficulty in integrally interpreting Chapter 4 and 5 is that the direction of MSE effect on the general cognition ability was still not well understood at the state-of-art level. Because our brain is complex not only in its temporal signal, but also from spatial and other aspects. As a newly emerging methodology, what does MSE exactly mean was still largely under exploration. In order to better understand this question, it's spatial complexity and association with different cognitive domains and frequency bands need to be further explored, which should be our future study direction.

Meanwhile, there's valuable significance of the whole study. First, it is study which systematically investigated under the framework of gene-brain-behavior using the most

advanced individual difference research methods at multiple measurement level. At the same time, we contributed for deeper understanding of complex brain signal which, in traditional studies, used to be largely regarded as meaningless noise. Brain signal complexity was the main topic investigated in my doctoral study and is receiving heated discussion during past several years. Exploration of underlying mechanism of brain signal complexity may largely help deepen the understanding of functional brain system and brain disorder. In my current study MSE was the main tool applied for indexing temporal brain signal complexity. Besides its association with cognitive ability and cognitive declination related genotype, its characterization of multiple social communicative ability may also be one of my future research interests, for example, the alteration in MSE indicated brain signal complexity when people were alone or under social condition. Measurements beyond MSE, such as microstate EEG (Koenig et al., 1999), could be further studied and applied for further investigation of spatio-temporal brain signal complexity.

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Declaration

Hiermit erkläre ich an Eides statt,

1. dass ich die vorliegende Arbeit selbständig und ohne unerlaubte Hilfe verfasst habe,

2. dass ich mich nicht anderwärts um einen Doktorgrad beworben habe und noch keinen Doktorgrad der Psychologie besitze,

3. dass mir die zugrunde liegende Promotionsordnung der Mathematisch Naturwissenschaftlichen Fakultät II vom 3.August 2006, veröffentlicht im Amtlichen Mitteilungsblatt Nr. 34/2006 bekannt ist.

Hong Kong, den

Li Xiaojing